

**DEPARTMENT OF  
VETERANS AFFAIRS**

**ANNUAL SUMMARY**

**Federally Sponsored Research on Gulf War  
Veterans' Illnesses for 2016**





# Annual Summary FY 2016

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## Federally Sponsored Research on Gulf War Veterans' Illnesses for 2016

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## **EXECUTIVE SUMMARY**

### **I. INTRODUCTION**

Section 707 of Public Law (P.L.) 102-585, as amended by section 104 of P.L. 105-368 and section 502 of P.L. 111-163, required that an annual report be submitted to the Senate and House Veterans' Affairs Committees through 2014 on the results, status, and priorities of research activities related to the health consequences of military service in the Gulf War (GW) in Operations Desert Shield and Desert Storm, 1990 and 1991. The Research Subcommittee of the interagency Deployment Health Working Group (DHWG) prepared the Annual Report to Congress on Federally Sponsored Research on Gulf War Veterans' Illnesses for 2014, which was the 21<sup>st</sup> report on Federal research and research activities. This report (2016) and last year's (2015) follow the general format of the earlier reports but are not required by Congress.

As in previous annual reports to Congress, the material presented is divided into six sections and three appendices. Section I is an introduction; Section II summarizes the research priorities and organization of the Federal GW research portfolio; Section III highlights and summarizes research progress published since the last annual report to Congress; Section IV summarizes Federal funding trends for GW research during the 10-year period from fiscal year (FY) 2007 through FY 2016; Section V highlights new research projects and initiatives since the last report; Section VI contains literature references; and the Appendices contain listings of federally-funded research projects.

### **II. RESEARCH PRIORITIES**

The research priorities remain unchanged from last year. The 19 Research Topics (two of the original 21 topics were eliminated in the 2006 annual report to Congress) are grouped into five major Research Focus Areas. These Research Focus Areas are used to organize Sections III and V, as well as Appendix B (Project Listing by Research Focus Area). In November 2005, at the request of the Secretary of Veterans Affairs, the Department of Veterans Affairs (VA) Office of Research and Development (ORD) developed a set of criteria for inclusion of VA-funded projects in the GW research portfolio and then evaluated the entire VA research portfolio for projects meeting those criteria. The criteria used as the basis for the review are presented in Section II.

### **III. PUBLISHED RESULTS AND STATUS OF THE FIELD IN 2015**

Section III provides abstracts or summaries of research articles on the health problems of GW Veterans published during calendar year (CY) 2016 or in CY 2015 after the previous annual summary was submitted.

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#### **IV. RESEARCH FUNDING TRENDS**

VA, the Department of Defense (DoD), and Department of Health and Human Services (HHS) funded 544 distinct projects from FY 1992 through FY 2016 related to health problems affecting GW Veterans. The scope of the Federal research portfolio is broad, from small pilot studies to large-scale epidemiology studies involving large populations and major center-based research programs. Federal funding for research on GWVI totaled almost \$280 million for the period from FY 2007 through FY 2016. As of September 30, 2016, 404 projects (74 percent of the 544 projects) were completed, and 140 projects (26 percent) were new or ongoing.

#### **V. NEW RESEARCH PROJECTS AND INITIATIVES**

Fifty-six new projects were funded through the FY 2016 appropriation or in CY 2015 after the previous annual summary was submitted for the Gulf War Illness Research Program (GWIRP) managed by the Congressionally Directed Medical Research Programs (CDMRP) at DoD. These projects focused on Brain and Nervous System Function (13), Environmental Toxicology (4), Symptoms and General Health (38), and Immune Function (1). VA funded eight new projects in FY 2016. One of these projects focused on Brain and Nervous System Function, and seven focused on Symptoms and General Health.

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## **I. INTRODUCTION**

The Secretary of Veterans Affairs was required by section 707 of P.L. 102-585, as amended by section 104 of P.L. 105-368 and section 502 of P.L. 111-163, to submit an annual report through 2014 on the results, status, and priorities of research activities related to the health consequences of military service in the GW to the Senate and House Committees on Veterans' Affairs. The Research Subcommittee of the interagency DHWG prepared the 2014 annual report to Congress, which was the 21<sup>st</sup> report on research and research activities (DHWG, 2004; DHWG, 2005; DHWG, 2006a; DHWG, 2006b; DHWG, 2007; DHWG, 2008; DHWG, 2009; DHWG, 2010; DHWG, 2011; DHWG, 2012; DHWG, 2013; DHWG, 2014; DHWG, 2015; MVHCB, 2001; MVHCB, 2002; PGVCB, 1995; PGVCB, 1996b; PGVCB, 1997; PGVCB, 1998; PGVCB, 1999; PGVCB, 2001). This report (2016) follows the general format of previous reports but is not required by Congress.

As in previous annual reports to Congress, the material presented is divided into six sections and three appendices. Section I is an introduction. Section II summarizes the research priorities and organization of the Federal GW research portfolio. Section III highlights and summarizes published research progress since the last report. Section IV summarizes Federal funding trends for GW research during the 10-year period from FY 2007 through FY 2016. Section V highlights new research projects and initiatives since the 2015 Annual Summary. Section VI contains literature references, and the Appendices contain listings of federally-funded research projects.

## **II. RESEARCH PRIORITIES**

### **A. Nineteen Research Topics**

The Persian Gulf Veterans Coordinating Board (PGVCB) was created in 1994 to coordinate research from VA, DoD, and HHS on GWVI. In 1995, the PGVCB devised a contextual framework for the results of completed and ongoing studies and also to develop an approach for the interpretation of research results. To that end, the PGVCB identified 19 major research questions and subsequently added two additional questions in 1996 (PGVCB, 1996a), to bring the total to 21. The comprehensive GW research portfolio has addressed each of these 21 questions, and relevant results have been published on each one. The Military and Veterans Health Coordinating Board (MVHCB), the successor organization to the PGVCB, conducted a comprehensive assessment of the progress made on each of these 21 questions in the 2000 annual report to Congress. The Research Subcommittee of the DHWG, which was established to address a broader range of deployment health issues, reviewed the 21 questions and replaced them with a corresponding list of 21 Research Topics for the 2004 annual report to Congress (DHWG, 2006a).

The original list of 21 questions has been reduced to 19. Based on the Institute of Medicine (IOM) of the National Academies review of the scientific literature on infectious diseases (Institute of Medicine, 2006b) and the state of our current scientific knowledge, the conclusion was reached in the 2006 annual report to Congress (DHWG, 2007) that there is no rationale to continue inclusion of infectious diseases as an area of research that

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will provide answers to the causes or cure for these symptoms. Questions 2 and 19 have, therefore, been removed from the original list of 21 Questions and the third Research Focus Area has been refocused from Immune Function and Infectious Diseases to just Immune Function. Projects originally identified as “GW research” under these two questions will continue to be listed in Appendices A and B, but no funding amounts will be shown for FY 2007 or beyond.

Similarly, projects related to Posttraumatic Stress Disorder (PTSD) that were originally included in the Federal GW research portfolio were closed as of FY 2007 (i.e., no funds listed in Appendix C) if they did not directly study a population of ill GW Veterans or were not investigating treatments that may prove beneficial for ill GW Veterans.

The IOM report reviewing the available literature on amyotrophic lateral sclerosis (ALS) in Veterans (Institute of Medicine, 2006a) concluded there is limited and suggestive evidence of an association between military service and later development of ALS. This strengthens the decision to include ALS as a relevant topic in the Federal portfolio of GW research (DHWG, 2006b). ALS projects included in the GW portfolio are primarily focused on epidemiologic studies in GW Veterans and the development of new methodologies to identify and treat ALS.

## **B. Research Portfolio Descriptors**

VA maintains a research database of federally sponsored research on GWVI. This includes research conducted by Federal scientists, as well as that by non-Federal scientists supported by Federal research funds through grants, contracts, and cooperative agreements. It is not possible to accurately track research efforts that fall within the private sector or otherwise outside of the purview of the Federal government.

**Appendix A** lists the projects that VA, DoD, and HHS have funded to date. Research projects are grouped according to the department that is responsible for funding. Dual-funded projects are listed under both departments.

**Appendix B** lists all federally-funded GW research projects regardless of the department providing the funding. Three descriptors are used to categorize each funded project.

The first descriptor is the primary **Research Focus Area** of the project. The five Research Focus Areas are also used to organize the 19 Research Topics (see Section A, above).

- Brain and Nervous System Function (e.g., studies on neurological or psychological deficits and/or alterations)
  - Organic neuropsychological and neurological deficits (original Question 16)
  - Psychological symptoms and/or diagnoses (original Question 18)
- Environmental Toxicology (e.g., studies focused on specific environmental exposures such as pesticides, oil well fires, jet fuel, vaccines, medical prophylactic agents, etc.)
  - Petroleum products and combustion products (original Question 3)

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- Occupational/environmental hazards (original Question 4)
  - Organophosphorus nerve agent and/or sulfur mustard from bombing at Muhammadiyah or weapons bunker at Khamisiyah (original Question 5)
  - Chemical agents, other than at Khamisiyah (original Question 6)
  - Pyridostigmine bromide (PB) and other medical prophylaxes (e.g., vaccines and anti-malarials) (original Question 7)
  - Psychophysiological stressors (original Question 8)
  - Short-term, low level exposures to PB, N, N-diethyl-m-toluamide (DEET), or permethrin, alone or in combination as a cause of short-term and/or long-term neurological effects (original Question 17)
- Immune Function (e.g., studies on alterations in immune function or host defenses)
    - Altered immune function or host defense (original Question 10)
  - Reproductive Health (e.g., studies on sexual and/or reproductive dysfunction)
    - Birth defects in offspring (original Question 11)
    - Lower reproductive success (original Question 12)
    - Sexual dysfunction (original Question 13)
  - Symptoms and General Health (e.g., studies on mortality, pulmonary disease, cancer, chronic multisymptom illnesses, etc.)
    - Increased prevalence or severity of symptoms and/or illnesses (original Question 1)
    - Nonspecific symptoms and symptom complexes (e.g., chronic multisymptom illnesses (CMI)) (original Question 9)
    - Changes in lung function or airway reactivity (original Question 14)
    - Smaller baseline lung function or greater degree of nonspecific airway reactivity (original Question 15)
    - Development of cancers of any type (original Question 20)
    - Mortality rates (original Question 21)

Secondary and/or tertiary Research Focus Areas from the above list may also be assigned. Two additional Research Focus Areas may be used for secondary and tertiary assignments. This permits accounting for projects that cover multiple focus areas.

- Chemical weapons (e.g., sarin, sulfur mustard, etc.)
- PB and other medical prophylaxes (e.g., vaccines, PB, antimalarials, etc.)

The second descriptor is the **Project Focus**, categorized as follows:

- Diagnosis: studies that will improve the ability to diagnose previously unexplained conditions or to better refine diagnoses with new tools
- Exposure: studies that examine individual exposures and/or interactions of exposures (chemical, biological, pharmacological, physiological, etc.)
- Interactions: interactions of combined exposures (chemical, biological, pharmacological, physiological, etc.)



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- Prevention: studies that will produce knowledge that could lead to disease prevention strategies
  - Symptoms: prevalence and risk factors for symptoms and alterations in general health status
  - Treatment: development or testing of new therapies

Each project is assigned up to three Project Focus areas as categorical descriptors. This allows accounting for projects that cover multiple focus areas. For example, a project on the neurophysiological effects of exposure to sarin in animals would have a focus on the brain and nervous system and a focus on chemical weapons. The number of focus areas (between one and three) assigned to a project depends on the project itself.

The third descriptor for each project is **Research Type**. Each research project on GWVI uses a method of approach to test a specific research hypothesis. Although precise categorization of research types can be difficult because of overlapping methodologies, research projects can be divided into the following general types:

MECHANISTIC: Research into underlying mechanisms of diseases and illnesses using in vitro and in vivo models.

CLINICAL: Application of an intervention, such as in a controlled drug trial, or use of methodologies such as case-control studies to define risk factors for disease.

EPIDEMIOLOGY: Study of the distribution and determinants of disease in human populations. It includes population-based studies focused on outcomes such as mortality, symptoms, hospitalizations, etc., using devices such as postal surveys, telephone interviews, and reviews of medical records.

DEVELOPMENT: In addition to tracking research on GWVI, the DHWG also tracks development activities. In general, development is the systematic use of the knowledge or understanding gained from research directed toward the production of materials; devices; systems; or methods, including design, development, and improvement of prototypes and new processes. Within the context of GWVI, the DHWG categorizes activities as development as an activity that satisfies the general definition of development described above and is directed toward new biologically based prevention, intervention, and treatment measures.

The research database on GWVI catalogs only research and development activities that either directly involve GW Veterans or answer specific questions about risk factors.

### **C. Portfolio Criteria**

In November 2005, at the request of the Secretary of Veterans Affairs, the VA ORD developed a set of criteria for inclusion of VA-funded projects in the GW research portfolio. The criteria and relevant references from that analysis are presented below. These criteria are now routinely used to identify relevant research projects. New projects selected for funding must meet these criteria and are presented in Section V.

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1. Studies of CMI affecting GW Veterans, including case definitions for CMI in GW Veterans and the general population.
    - a) Case definitions of multisymptom illnesses affecting GW Veterans (Fukuda et al., 1998; Haley et al., 1997a; Haley et al., 1997b; Haley et al., 2002; Steele, 2000; Wolfe et al., 2002; IOM, 2014)
    - b) Chronic fatigue syndrome (Dunphy et al., 2003; Eisen et al., 2005; Gray et al., 2002; The Iowa Persian Gulf Study Group, 1997; Unwin et al., 1999)
    - c) Fibromyalgia (Eisen et al., 2005; The Iowa Persian Gulf Study Group, 1997)
    - d) Irritable bowel syndrome (Dunphy et al., 2003; Gray et al., 2002; The Iowa Persian Gulf Study Group, 1997)
    - e) Multiple chemical sensitivity (MCS) (Fiedler et al., 2004; Gray et al., 2002; The Iowa Persian Gulf Study Group, 1997)
  2. Conditions and/or symptoms occurring with higher prevalence in GW Veterans
    - a) Fatigue (CDC, 1995; Coker et al., 1999; Doebbeling et al., 2000; Fukuda et al., 1998; Gray et al., 1999; Haley et al., 1997b; The Iowa Persian Gulf Study Group, 1997; Unwin et al., 1999; Wolfe et al., 2002)
    - b) Joint and muscle pain (CDC, 1995; Coker et al., 1999; Fukuda et al., 1998; Gray et al., 1999; Haley et al., 1997a; Haley et al., 1997b; Haley, 2003; Kang et al., 2000; Pierce, 1997; Proctor et al., 1998; The Iowa Persian Gulf Study Group, 1997; Wolfe et al., 2002)
    - c) Gastrointestinal complaints (dyspepsia, gastritis, diarrhea, etc.) (Blanchard et al., 2006; CDC, 1995; Coker et al., 1999; Eisen et al., 2005; Fukuda et al., 1998; Gray et al., 2002; Haley et al., 1997b; Kang et al., 2000; Proctor et al., 1998)
    - d) Cognitive dysfunction (memory, attention, etc.) (CDC, 1995; Coker et al., 1999; Fukuda et al., 1998; Gray et al., 1999; Haley et al., 1997b; Kang et al., 2000; Knoke et al., 2000; Proctor et al., 1998; The Iowa Persian Gulf Study Group, 1997; Wolfe et al., 2002)
    - e) Sleep disturbances (CDC, 1995; Coker et al., 1999; Gray et al., 1999; Haley et al., 1997b; Kang et al., 2000; Knoke et al., 2000; Pierce, 1997; Proctor et al., 1998; Unwin et al., 1999; Wolfe et al., 2002)
    - f) Central Nervous System disorders (ALS, glioblastoma, imaging studies, etc.) (Bullman et al., 2005; Haley, 2003; Horner et al., 2003; Weisskopf et al., 2005)
    - g) Headaches (CDC, 1995; Coker et al., 1999; Fukuda et al., 1998; Gray et al., 1999; Haley et al., 1997b; Kang et al., 2000; Knoke et al., 2000; Proctor et al., 1998; Unwin et al., 1999; Wolfe et al., 2002)
    - h) Dermatologic conditions (CDC, 1995; Coker et al., 1999; Eisen et al., 2005; Fukuda et al., 1998; Gray et al.,

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1999; Kang et al., 2000; Knoke et al., 2000; Pierce, 1997; Proctor et al., 1998; Wolfe et al., 2002)

3. Long-term health effects of potentially hazardous substances, alone and in combination, to which GW Veterans may have been exposed to during deployment
  - a) PB  
(Abou-Donia et al., 1996; Haley et al., 1997c; Wolfe et al., 2002; Abdel-Rahman et al., 2004)
  - b) DEET  
(Abou-Donia et al., 1996; Haley et al., 1997c; Wolfe et al., 2002; Abdel-Rahman et al., 2004)
  - c) Permethrin  
(Abou-Donia et al., 1996; Haley et al., 1997c; Wolfe et al., 2002; Abdel-Rahman et al., 2004)
  - d) Oil well fire smoke  
(Poirier et al., 1998; Lange et al., 2002)
  - e) Petroleum products (e.g., jet fuels) and combustion products  
(Peden-Adam et al., 2001; Bell et al., 2005)
  - f) Multiple vaccinations and other medical prophylaxes  
(Rook et al., 1997; Hotopf et al., 2000; Kang et al., 2000)
4. Other topics from the 19 Topics forming the framework for the *Annual Report to Congress on Federally Sponsored Research on GW Veterans' Illnesses*:
  - a) Altered immune function and/or host defense  
(Zhang et al., 1999; Peden-Adam et al., 2001)
  - b) Physiological responses to biological stress  
(Abdel-Rahman et al., 2004; Fiedler et al., 2004)
  - c) Sexual and/or reproductive dysfunction  
(Cowan et al., 1997; Doyle et al., 1997; The Iowa Persian Gulf Study Group, 1997)

### **III. PUBLISHED RESULTS AND STATUS OF THE FIELD IN 2015**

#### **A. Summary**

Since the 2015 Annual Summary, numerous research studies have provided new and detailed information on the health problems of GW Veterans. A PubMed search retrieved 51 relevant articles published in English in calendar year 2016 or in 2015 after the last report was submitted. These articles include federally and non-federally funded research, as well as international research. Most of the articles are related to more than one of the five Research Focus Areas described in Section II. B., above. However, fourteen can be characterized as Brain and Nervous System Function, twenty-seven as Symptoms and General Health, eight as Environmental Toxicology, and two as Immune Dysfunction. No articles regarding Reproductive Health were found for 2016.

#### **B. Abstracts/Summaries from Published Research**

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**Abdullah L, Evans JE, Joshi U, Crynen G, Reed J, Mouzon B, Baumann S, Montague H, Zakirova Z, Emmerich T, Bachmeier C, Klimas N, Sullivan K, Mullan M, Ait-Ghezala G, Crawford F. Translational potential of long-term decreases in mitochondrial lipids in a mouse model of Gulf War Illness. *Toxicol.* 2016 Nov 30;372:22-33. doi: 10.1016/j.tox.2016.10.012. Epub 2016 Oct 29.**

Gulf War Illness (GWI) affects 25% of veterans from the 1990-1991 Gulf War (GW) and is accompanied by damage to the brain regions involved in memory processing. After twenty-five years, the chronic pathobiology of GWI is still unexplained. To address this problem, we examined the long-term consequences of GW exposures in an established GWI mouse model to identify biological processes that are relevant to the chronic symptoms of GWI. Three-month old male C57BL6 mice were exposed for 10 days to GW agents (pyridostigmine bromide and permethrin). Barnes Maze testing conducted at 15- and 16-months post-exposure revealed learning and memory impairment. Immunohistochemical analyses showed astroglia and microglia activation in the hippocampi of exposed mice. Proteomic studies identified perturbation of mitochondria function and metabolomics data showed decreases in the Krebs cycle compounds, lactate,  $\beta$ -hydroxybutyrate and glycerol-3 phosphate in the brains of exposed mice. Lipidomics data showed decreases in fatty acids, acylcarnitines and phospholipids, including cardiolipins in the brains of exposed mice. Pilot biomarker studies showed that plasma from exposed mice and veterans with GWI had increases in odd-chain, and decreases in long-chain, acylcarnitines compared to their respective controls. Very long-chain acylcarnitines were decreased in veterans with GWI compared to controls. These studies suggest that mitochondrial lipid disturbances might be associated with GWI and that further investigation is required to determine its role in the pathophysiology of this illness. Targeting mitochondrial function may provide effective therapies for GWI, and that lipid abnormalities could serve as biomarkers of GWI.

**Albrecht PJ, Rice FL. Fibromyalgia syndrome pathology and environmental influences on afflictions with medically unexplained symptoms. *Rev Environ Health.* 2016 Jun 1;31(2):281-94. doi: 10.1515/reveh-2015-0040. Review.**

Fibromyalgia syndrome (FMS) is a clinical disorder predominant in females with unknown etiology and medically unexplained symptoms (MUS), similar to other afflictions, including irritable bowel syndrome (IBS), chronic fatigue syndrome (CFS), post-traumatic stress disorder (PTSD), Gulf War illness (GWI), and others. External environmental stimuli drive behavior and impact physiologic homeostasis (internal environment) via autonomic functioning. These environments directly impact the individual affective state (mind), which feeds back to regulate physiology (body). FMS has emerged as a complex disorder with pathologies identified among neurotransmitter and enzyme levels, immune/cytokine functionality, cortical volumes, cutaneous innervation, as well as an increased frequency among people with a history of traumatic and/or emotionally negative events, and specific personality trait profiles. Yet, quantitative physical evidence of pathology or disease etiology among FMS has been limited (as with other afflictions with MUS). Previously, our group published findings of increased peptidergic sensory innervation associated with the arterio-venous shunts (AVS) in the glabrous hand skin of FMS patients, which provides a plausible mechanism for the wide-spread FMS symptomology. This review focuses on

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FMS as a model affliction with MUS to discuss the implications of the recently discovered peripheral innervation alterations, explore the role of peripheral innervation to central sensitization syndromes (CSS), and examine possible estrogen-related mechanisms through which external and internal environmental factors may contribute to FMS etiology and possibly other afflictions with MUS.

**Al-Shammari AM. Environmental pollutions associated to conflicts in Iraq and related health problems. Rev Environ Health. 2016 Jun 1;31(2):245-50. doi: 10.1515/reveh-2015-0024. Review.**

Several wars and a 13-year embargo as well as several years of civil war with the recent war on terrorism have cumulatively damaged Iraq's land, air, water, and health infrastructure. The sand particles in Iraq contain toxic substances, which dates back to the pollution caused by military actions that disassemble the desert sands and turn it into light dust. This dust reaches cities as dust storms that effect most Iraqi cities. The presence of depleted uranium (DU) in the Iraqi food chain is documented by measuring the uranium in animals organs in different Iraqi cities with the highest concentration in the south of Iraq. One of the major sites of pollution in Iraq is the Al-twaitha nuclear research site. The nuclear research reactors were destroyed in the 1991 Gulf War. Barrels containing radioactive materials and sources were stolen from the site in the 2003 war. This resulted in considerable radioactive pollution at the site and in its surrounding areas. Soil sample have been found to be contaminated by Cs-137 and Co-60. Cancer and birth defects are most associated with the environmental pollution caused by the conflicts. All studies related to this by Iraqi researchers are discussed in this review. From studying the Iraqi scientific publications, we can conclude that Basrah, Baghdad, Faluja, Mosul and Thi-Qar are the most effected cities in Iraq. This review concludes that the presence of a heavily contaminated environment with war related pollutants in most of the Iraqi cities needs much attention and huge effort to reduce the related health problems.

**Barth SK, Kang HK, Bullman T. All-Cause Mortality Among US Veterans of the Persian Gulf War: 13-Year Follow-up. Public Health Rep. 2016 Nov;131(6):822-830. doi: 10.1177/0033354916676278. Epub 2016 Oct 27.**

**OBJECTIVE:** We determined cause-specific mortality prevalence and risks of Gulf War deployed and nondeployed veterans to determine if deployed veterans were at greater risk than nondeployed veterans for death overall or because of certain diseases or conditions up to 13 years after conflict subsided. **METHODS:** Follow-up began when the veteran left the Gulf War theater or May 1, 1991, and ended on the date of death or December 31, 2004. We studied 621 901 veterans who served in the 1990-1991 Persian Gulf War and 746 247 veterans who served but were not deployed during the Gulf War. We used Cox proportional hazard models to calculate rate ratios adjusted for age at entry to follow-up, length of follow-up, race, sex, branch of service, and military unit. We compared the mortality of (1) Gulf War veterans with non-Gulf War veterans and (2) Gulf War army veterans potentially exposed to nerve agents at Khamisiyah in March 1991 with those not exposed. We compared standardized mortality ratios of deployed and nondeployed Gulf War veterans with the US population. **RESULTS:** Male Gulf War veterans had a lower

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risk of mortality than male non-Gulf War veterans (adjusted rate ratio [aRR] = 0.97; 95% confidence interval [CI], 0.95-0.99), and female Gulf War veterans had a higher risk of mortality than female non-Gulf War veterans (aRR = 1.15; 95% CI, 1.03-1.28). Khamisiyah-exposed Gulf War army veterans had >3 times the risk of mortality from cirrhosis of the liver than nonexposed army Gulf War veterans (aRR = 3.73; 95% CI, 1.64-8.48). Compared with the US population, female Gulf War veterans had a 60% higher risk of suicide and male Gulf War veterans had a lower risk of suicide (standardized mortality ratio = 0.84; 95% CI, 0.80-0.88). CONCLUSION: The vital status and mortality risk of Gulf War and non-Gulf War veterans should continue to be investigated.

**Bomyea J, Lang AJ, Delano-Wood L, Jak A, Hanson KL, Sorg S, Clark AL, Schiehser DM. Neuropsychiatric Predictors of Post-Injury Headache After Mild-Moderate Traumatic Brain Injury in Veterans. Headache. 2016 Apr;56(4):699-710. doi: 10.1111/head.12799. Epub 2016 Mar 29.**

**OBJECTIVES:** To determine differences in neuropsychiatric complaints between Veterans with mild to moderate traumatic brain injury (TBI), with and without headache, compared with Veteran controls, and to identify neuropsychiatric predictors of headache severity. **BACKGROUND:** Mild to moderate TBI is a common occurrence in Veterans, and is frequently associated with complaints of headache. Neuropsychiatric complaints are also common among individuals who have sustained head injury, although the relationship between these factors and headache after injury is unclear. Research is needed to comprehensively determine differences between individuals with mild to moderate traumatic brain injury who differ with respect to headache, and which injury, psychological, or sleep and fatigue factors predict headache severity. **METHODS:** A cross-sectional study compared 85 Veterans in three groups (positive for TBI and headache, positive for TBI without significant headache, and a control group) on a set of injury characteristics and neuropsychiatric variables. Correlates of headache severity were examined, and a regression model was used to identify significant independent predictors of headache severity. **RESULTS:** Individuals with mild to moderate TBI and headache endorsed significantly greater neuropsychiatric symptoms than participants in the other groups ( $\eta(p)^2 = .23-.36$ ) Neuropsychiatric complaints, as well as presence of posttraumatic amnesia, were correlated with headache in the subsample with TBI ( $r_s = .44-.57$ ). When entering all predictors into a regression model, only fatigue represented a significant independent predictor of headache severity ( $\beta = .59$ ,  $R^2 = .35$ ). **CONCLUSIONS:** Rather than being a global risk factor, mild to moderate TBI was associated with poorer mental health outcomes, particularly for those who endorse headache. Findings underscore the possibility that Veterans with history of TBI who present with complaints of headache may represent a particularly vulnerable subgroup. Additionally, our findings suggest that clinical outcomes may be improved in those with neurotrauma by incorporating a focus on fatigue in treatment.

**Cange CW. The life course model as a framework for post-conflict health analysis: reflections on the Gulf War critical period. Med Confl Surviv. 2016 Oct-Dec;32(4):282-294. doi: 10.1080/13623699.2016.1269284. Epub 2017 Jan 3.**

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In the Kuwait context, from January 1991 to December 1991, there were a series of chemical and psychological Gulf War-era exposures that left persistent, long-term damage. Extreme stress from a critical event speeds up the usual disease latency period, and may be part of a synergistic effect that leads to higher disease rates over a shorter period of time. I am interested in the impact of armed conflict on health outcomes over the life course in Kuwait, and particularly the pathways through which armed conflict causes changes in health on a population level. In this paper, I propose a culturally sensitive, post-conflict socio-ecological model that informs a three-pronged health study. I propose a macro-micro mix that includes an ecological study, a case-control study and a qualitative study to investigate Kuwait's post-conflict health concerns. Thus, I revise the concept of 'post-conflict health' as a trajectory that is mediated through different, complex social levels and develops over time during the latency period. The main advantage of a macro-micro mix approach for post-conflict health is that it contextualizes the Gulf War as an environmental health issue.

**Chao LL, Abadjian LR, Esparza IL, Reeb R. Insomnia Severity, Subjective Sleep Quality, and Risk for Obstructive Sleep Apnea in Veterans With Gulf War Illness. *Mil Med.* 2016 Sep;181(9):1127-34. doi: 10.7205/MILMED-D-15-00474.**

Despite the fact that sleep disturbances are common in veterans with Gulf War Illness (GWI), there has been a paucity of published sleep studies in this veteran population to date. Therefore, the present study examined subjective sleep quality (assessed with the Pittsburgh Sleep Quality Index), insomnia severity (assessed with the Insomnia Severity Index), and risk for obstructive sleep apnea (assessed with the STOP questionnaire) in 98 Gulf War veterans. Veterans with GWI, defined either by the Kansas or Centers for Disease Control and Prevention criteria, had greater risk for obstructive sleep apnea (i.e., higher STOP scores) than veterans without GWI. This difference persisted even after accounting for potentially confounding demographic (e.g., age, gender) and clinical variables. Veterans with GWI, defined by either the Kansas or Centers for Disease Control and Prevention criteria, also had significantly greater insomnia severity and poorer sleep quality than veterans without GWI ( $p < 0.05$ ), even after accounting for potentially confounding variables. Furthermore, there were significant, positive correlations between insomnia severity, subjective sleep quality, and GWI symptom severity ( $p \leq 0.01$ ). In stepwise linear regression models, insomnia severity significantly predicted GWI status over and above demographic and clinical variables. Together these findings provide good rationale for treating sleep disturbances in the management of GWI.

**Chao LL, Reeb R, Esparza IL, Abadjian LR. Associations between the self-reported frequency of hearing chemical alarms in theater and regional brain volume in Gulf War Veterans. *Neurotoxicol.* 2016 Mar;53:246-256. doi: 10.1016/j.neuro.2016.02.009. Epub 2016 Feb 23.**

**BACKGROUND:** We previously reported evidence of reduced cortical gray matter (GM), white matter (WM), and hippocampal volume in Gulf War (GW) veterans with predicted exposure to low-levels of nerve agent according to the 2000 Khamisiyah plume model analysis. Because there is suggestive evidence that other nerve agent exposures may

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have occurred during the Gulf War, we examined the association between the self-reported frequency of hearing chemical alarms sound during deployment in the Gulf War and regional brain volume in GW veterans. **METHODS:** Ninety consecutive GW veterans (15 female, mean age: 52±8years) participating in a VA-funded study underwent structural magnetic resonance imaging (MRI) on a 3T scanner. Freesurfer (version 5.1) was used to obtain regional measures of cortical GM, WM, hippocampal, and insula volume. Multiple linear regression was used to determine the association between the self-reported frequencies of hearing chemical alarms during the Gulf War and regional brain volume. **RESULTS:** There was an inverse association between the self-reported frequency of hearing chemical alarms sound and total cortical GM (adjusted  $p=0.007$ ), even after accounting for potentially confounding demographic and clinical variables, the veterans' current health status, and other concurrent deployment-related exposures that were correlated with hearing chemical alarms. Post-hoc analyses extended the inverse relationship between the frequency of hearing chemical alarms to GM volume in the frontal (adjusted  $p=0.02$ ), parietal (adjusted  $p=0.01$ ), and occipital (adjusted  $p=0.001$ ) lobes. In contrast, regional brain volumes were not significantly associated with predicted exposure to the Khamisiyah plume or with Gulf War Illness status defined by the Kansas or Centers for Disease Control and Prevention criteria. **CONCLUSIONS:** Many veterans reported hearing chemical alarms sound during the Gulf War. The current findings suggest that exposure to substances that triggered those chemical alarms during the Gulf War likely had adverse neuroanatomical effects.

**Chao LL. Associations Between the Self-Reported Frequency of Hearing Chemical Alarms in Theater and Visuospatial Function in Gulf War Veterans. J Occup Environ Med. 2016 Oct;58(10):1014-1020.**

**OBJECTIVE:** The aim of this study was to examine the relationship between the self-reported frequencies of hearing chemical alarms during deployment and visuospatial function in Gulf War (GW) veterans. **METHODS:** The relationship between the self-reported frequency of hearing chemical alarms, neurobehavioral, and volumetric brain imaging data was examined with correlational, regression, and mediation analyses. **RESULTS:** The self-reported frequency of hearing chemical alarms was inversely associated with and significantly predicted performance on a visuospatial task (ie, Block Design) over and above potentially confounding variables, including concurrent, correlated GW-related exposures. This effect was partially mediated by the relationship between hearing chemical alarms and lateral occipital cortex volume. **CONCLUSIONS:** Exposure to substances that triggered chemical alarms during GW deployment likely had adverse effects on veterans' brain structure and function, warranting further investigation of whether these GW veterans are at an increased risk for dementia.

**Chen P, Miah MR, Aschner M. Metals and Neurodegeneration. F1000Res. 2016 Mar 17;5. pii: F1000 Faculty Rev-366. doi: 10.12688/f1000research.7431.1. eCollection 2016. Review.**

Metals play important roles in the human body, maintaining cell structure and regulating gene expression, neurotransmission, and antioxidant response, to name a few. However,



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excessive metal accumulation in the nervous system may be toxic, inducing oxidative stress, disrupting mitochondrial function, and impairing the activity of numerous enzymes. Damage caused by metal accumulation may result in permanent injuries, including severe neurological disorders. Epidemiological and clinical studies have shown a strong correlation between aberrant metal exposure and a number of neurological diseases, including Alzheimer's disease, amyotrophic lateral sclerosis, autism spectrum disorders, Guillain-Barré disease, Gulf War syndrome, Huntington's disease, multiple sclerosis, Parkinson's disease, and Wilson's disease. Here, we briefly survey the literature relating to the role of metals in neurodegeneration.

**Conboy L, Gerke T, Hsu KY, St John M, Goldstein M, Schnyer R. The Effectiveness of Individualized Acupuncture Protocols in the Treatment of Gulf War Illness: A Pragmatic Randomized Clinical Trial. PLoS One. 2016 Mar 31;11(3):e0149161. doi: 10.1371/journal.pone.0149161. eCollection 2016.**

**BACKGROUND:** Gulf War Illness is a Complex Medical Illness characterized by multiple symptoms, including fatigue, sleep and mood disturbances, cognitive dysfunction, and musculoskeletal pain affecting veterans of the first Gulf War. No standard of care treatment exists. **METHODS:** This pragmatic Randomized Clinical Trial tested the effects of individualized acupuncture treatments offered in extant acupuncture practices in the community; practitioners had at least 5 years of experience plus additional training provided by the study. Veterans with diagnosed symptoms of Gulf War Illness were randomized to either six months of biweekly acupuncture treatments (group 1, n = 52) or 2 months of waitlist followed by weekly acupuncture treatments (group 2, n = 52). Measurements were taken at baseline, 2, 4 and 6 months. The primary outcome is the SF-36 physical component scale score (SF-36P) and the secondary outcome is the McGill Pain scale. **RESULTS:** Of the 104 subjects who underwent randomization, 85 completed the protocol (82%). A clinically and statistically significant average improvement of 9.4 points ( $p = 0.03$ ) in the SF-36P was observed for group 1 at month 6 compared to group 2, adjusting for baseline pain. The secondary outcome of McGill pain index produced similar results; at 6 months, group 1 was estimated to experience a reduction of approximately 3.6 points ( $p = 0.04$ ) compared to group 2. **CONCLUSIONS:** Individualized acupuncture treatment of sufficient dose appears to offer significant relief of physical disability and pain for veterans with Gulf War Illness.

**Cooper BY, Johnson RD, Nutter TJ. Exposure to Gulf War Illness chemicals induces functional muscarinic receptor maladaptations in muscle nociceptors. Neurotoxicology. 2016 May;54:99-110. doi: 10.1016/j.neuro.2016.04.001. Epub 2016 Apr 4.**

Chronic pain is a component of the multisymptom disease known as Gulf War Illness (GWI). There is evidence that pain symptoms could have been a consequence of prolonged and/or excessive exposure to anticholinesterases and other GW chemicals. We previously reported that rats exposed, for 8 weeks, to a mixture of anticholinesterases (pyridostigmine bromide, chlorpyrifos) and a Nav (voltage activated Na(+)) channel deactivation-inhibiting pyrethroid, permethrin, exhibited a behavior pattern that was

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consistent with a delayed myalgia. This myalgia-like behavior was accompanied by persistent changes to Kv (voltage activated K(+)) channel physiology in muscle nociceptors (Kv7, KDR). In the present study, we examined how exposure to the above agents altered the reactivity of Kv channels to a muscarinic receptor (mAChR) agonist (oxotremorine-M). Comparisons between muscle nociceptors harvested from vehicle and GW chemical-exposed rats revealed that mAChR suppression of Kv7 activity was enhanced in exposed rats. Yet in these same muscle nociceptors, a Stromatotoxin-insensitive component of the KDR (voltage activated delayed rectifier K(+) channel) exhibited decreased sensitivity to activation of mAChR. We have previously shown that a unique mAChR-induced depolarization and burst discharge (MDBD) was exaggerated in muscle nociceptors of rats exposed to GW chemicals. We now provide evidence that both muscle and vascular nociceptors of naïve rats exhibit MDBD. Examination of the molecular basis of the MDBD in naïve animals revealed that while the mAChR depolarization was independent of Kv7, the action potential burst was modulated by Kv7 status. mAChR depolarizations were shown to be dependent, in part, on TRPA1. We argue that dysfunction of the MDBD could be a functional convergence point for maladapted ion channels and receptors consequent to exposure to GW chemicals.

**Cooper CM, Briggs RW, Farris EA, Bartlett J, Haley RW, Odegard TN. Memory and functional brain differences in a national sample of U.S. veterans with Gulf War Illness. *Psychiatry Res.* 2016 Apr 30;250:33-41. doi: 10.1016/j.psychres.2016.03.004. Epub 2016 Mar 18.**

Roughly 26-32% of U. S. veterans who served in the 1991 Persian Gulf War report suffering from chronic health problems. Memory complaints are regularly reported by ill Gulf War veterans (GWV), but limited data verify their complaints. This study investigated episodic memory and brain function in a nationally representative sample of GWV, using a face-name memory task and functional magnetic resonance imaging during encoding. A syndrome classification system was used to subdivide ill GWV into the three major Gulf War Illness syndrome types, "impaired cognition" (GWV-1), "confusion ataxia" (GWV-2), and "central pain" (GWV-3). Memory and brain function of ill GWV were contrasted to deployed and nondeployed well GWV controls (GWV-C). Ill GWV exhibited impaired memory function relative to GWV-C but the patterns of functional brain differences varied. Brain activation differentiated the GWV-C from the ill GWV. The different syndrome types also differed from one another in several brain regions. Additionally, the current study was the first to observe differences in brain function between deployed and nondeployed GWV-C. These results provide (1) evidence of memory impairment in ill GWV and differentiate the syndrome types at a functional neurobiological level, and (2) the role of deployment in the war on brain function.

**Coughlin SS. Need for Studies of the Health of Gulf War Women Veterans. *Mil Med.* 2016 Mar;181(3):198. doi: 10.7205/MILMED-D-15-00563. Letter; No abstract available.**

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**Coughlin SS. Physical Activity and Chronic Illnesses among Gulf War Veterans. Ann Transl Med Epidemiol. 2016;3(1). pii: 1010. Epub 2016 Oct 6. Editorial; No abstract available.**

**Coughlin SS. Results From the Follow-Up Study of a National Cohort of Gulf War and Gulf Era Veterans. J Occup Environ Med. 2016 May;58(5):e186. doi: 10.1097/JOM.0000000000000721. Comment; No abstract available.**

**Department of Veterans Affairs. Extension of the Presumptive Period for Compensation for Gulf War Veterans. Interim final rule. Fed Regist. 2016 Oct 17;81(200):71382-4.**

The Department of Veterans Affairs (VA) is issuing this final rule to affirm its adjudication regulations regarding compensation for disabilities resulting from undiagnosed illnesses suffered by veterans who served in the Persian Gulf War. This amendment is necessary to extend the period during which disabilities associated with undiagnosed illnesses and medically unexplained chronic multi-symptom illnesses must become manifest in order for a Veteran to be eligible for compensation. The intended effect of this amendment is to provide consistency in VA adjudication policy, preserve certain rights afforded to Persian Gulf War (GW) veterans, and ensure fairness for current and future GW veterans.

**Deshpande LS, Blair RE, Huang BA, Phillips KF, DeLorenzo RJ. Pharmacological blockade of the calcium plateau provides neuroprotection following organophosphate paraoxon induced status epilepticus in rats. Neurotoxicol Teratol. 2016 Jul-Aug;56:81-86. doi: 10.1016/j.ntt.2016.05.002. Epub 2016 May 17.**

Organophosphate (OP) compounds which include nerve agents and pesticides are considered chemical threat agents. Currently approved antidotes are crucial in limiting OP mediated acute mortality. However, survivors of lethal OP exposure exhibit delayed neuronal injury and chronic behavioral morbidities. In this study, we investigated neuroprotective capabilities of dantrolene and carisbamate in a rat survival model of paraoxon (POX) induced status epilepticus (SE). Significant elevations in hippocampal calcium levels were observed 48-h post POX SE survival, and treatment with dantrolene (10 mg/kg, i.m.) and carisbamate (90 mg/kg, i.m.) lowered these protracted calcium elevations. POX SE induced delayed neuronal injury as characterized by Fluoro Jade C labeling was observed in critical brain areas including the dentate gyrus, parietal cortex, amygdala, and thalamus. Dantrolene and carisbamate treatment provided significant neuroprotection against delayed neuronal damage in these brain regions when administered one-hour after POX-SE. These results indicate that dantrolene or carisbamate could be effective adjuvant therapies to the existing countermeasures to reduce neuronal injury and behavioral morbidities post OP SE survival.

**Deshpande LS, Blair RE, Phillips KF, DeLorenzo RJ. Role of the calcium plateau in neuronal injury and behavioral morbidities following organophosphate intoxication. Ann N Y Acad Sci. 2016 Jun;1374(1):176-83. doi: 10.1111/nyas.13122. Epub 2016 Jun 21. Review.**

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Organophosphate (OP) chemicals include nerve agents and pesticides, and there is a growing concern of OP-based chemical attacks against civilians. Current antidotes are essential in limiting immediate mortality associated with OP exposure. However, further research is needed to identify the molecular mechanisms underlying long-term neurological deficits following survival of OP toxicity in order to develop effective therapeutics. We have developed rat survival models of OP-induced status epilepticus (SE) that mimic chronic mortality and morbidity following OP intoxication. We have observed significant elevations in hippocampal calcium levels after OP SE that persisted for weeks following initial survival. Drugs inhibiting intracellular calcium-induced calcium release, such as dantrolene, levetiracetam, and carisbamate, lowered OP SE-mediated protracted calcium elevations. Given the critical role of calcium signaling in modulating behavior and cell death mechanisms, drugs targeted at preventing the development of the calcium plateau could enhance neuroprotection, help reduce morbidity, and improve outcomes following survival of OP SE.

**Dursa EK, Barth SK, Schneiderman AI, Bossarte RM. Physical and Mental Health Status of Gulf War and Gulf Era Veterans: Results From a Large Population-Based Epidemiological Study. J Occup Environ Med. 2016 Jan;58(1):41-6. doi: 10.1097/JOM.0000000000000627.**

**OBJECTIVE:** The aim of the study was to report the mental and physical health of a population-based cohort of Gulf War and Gulf Era veterans 20 years after the war. **METHODS:** A multimode (mail, Web, or computer-assisted telephone interviewing) health survey of 14,252 Gulf War and Gulf Era veterans. The survey consisted of questions about general, physical, mental, reproductive, and functional health. **RESULTS:** Gulf War veterans report a higher prevalence of almost all queried physical and mental health conditions. The population as a whole, however, has a significant burden of disease including high body mass index and multiple comorbid conditions. **CONCLUSIONS:** Gulf War veterans continue to report poorer health than Gulf Era veterans, 20 years after the war. Chronic disease management and interventions to improve health and wellness among both Gulf War and Gulf Era veterans are necessary.

**Dursa EK, Barth SK, Schneiderman AI, Bossarte RM. Physical and Mental Health Status of Gulf War and Gulf Era Veterans: Results From a Large Population-Based Epidemiological Study. J Occup Environ Med. 2016 May;58(5):e187. Reply to Comment; No abstract available.**

**Engdahl BE, James LM, Miller RD, Leuthold AC, Lewis SM, Carpenter AF, Georgopoulos AP. A Magnetoencephalographic (MEG) Study of Gulf War Illness (GWI). EBioMedicine. 2016 Oct;12:127-132. doi: 10.1016/j.ebiom.2016.08.030. Epub 2016 Aug 22.**

**BACKGROUND:** Gulf War Illness (GWI) has affected many Gulf War veterans. It involves several organs, most notably the brain. Neurological-cognitive-mood-related symptoms frequently dominate and are at the root of chronic ill-health and disability in GWI. Here we

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investigated the neural mechanisms underlying brain dysfunction in GWI in the absence of mental health disorders. **METHODS:** Eighty-six veterans completed diagnostic interviews to establish the presence of GWI and assess mental health status. Participants diagnosed with GWI met both Center for Disease Control and Kansas criteria. We studied 46 healthy controls and 40 veterans with GWI without mental illness. They all underwent a resting-state magnetoencephalographic (MEG) scan to assess brain communication based on synchronous neural interactions (SNI; Georgopoulos et al., 2007). **FINDINGS:** We found substantial differences in SNI between control and GWI groups centered on the cerebellum and frontal cortex. In addition, using the maxima and minima of SNI per sensor as predictors, we successfully classified 94.2% of the 86 participants (95% sensitivity, 93.5% specificity). **INTERPRETATION:** These findings document distinct differences in brain function between control and GWI in the absence of mental health comorbidities, differences that are excellent predictors of GWI.

**Flunker LK, Nutter TJ, Johnson RD, Cooper BY. DEET potentiates the development and persistence of anticholinesterase dependent chronic pain signs in a rat model of Gulf War Illness pain. Toxicol Appl Pharmacol. 2017 Feb 1;316:48-62. doi: 10.1016/j.taap.2016.12.014. Epub 2016 Dec 23.**

Exposure to DEET (N,N-diethyl-meta-toluamide) may have influenced the pattern of symptoms observed in soldiers with GWI (Gulf War Illness; Haley and Kurt, 1997). We examined how the addition of DEET (400mg/kg; 50% topical) to an exposure protocol of permethrin (2.6mg/kg; topical), chlorpyrifos (CP; 120mg/kg), and pyridostigmine bromide (PB; 13mg/kg) altered the emergence and pattern of pain signs in an animal model of GWI pain (Nutter et al., 2015). Rats underwent behavioral testing before, during and after a 4week exposure: 1) hindlimb pressure withdrawal threshold; 2) ambulation (movement distance and rate); and 3) resting duration. Additional studies were conducted to assess the influence of acute DEET (10-100 $\mu$ M) on muscle and vascular nociceptor K<sub>v</sub>7, K<sub>DR</sub>, Nav1.8 and Nav1.9. We report that a 50% concentration of DEET enhanced the development and persistence of pain-signs. Rats exposed to all 4 compounds exhibited ambulation deficits that appeared 5-12weeks post-exposure and persisted through weeks 21-24. Rats exposed to only three agents (CP or PB excluded), did not fully develop ambulation deficits. When PB was excluded, rats also developed rest duration pain signs, in addition to ambulation deficits. There was no evidence that physiological doses of DEET acutely modified nociceptor K<sub>v</sub>7, K<sub>DR</sub>, Nav1.8 or Nav1.9 activities. Nevertheless, DEET augmented protocols decreased the conductance of K<sub>v</sub>7 expressed in vascular nociceptors harvested from chronically exposed rats. We concluded that DEET enhanced the development and persistence of pain behaviors, but the anticholinesterases CP and PB played a determinant role.

**Fox AB, Walker BE, Smith BN, King DW, King LA, Vogt D. Understanding how deployment experiences change over time: Comparison of female and male OEF/OIF and Gulf War veterans. Psychol Trauma. 2016 Mar;8(2):135-40. doi: 10.1037/tra0000033. Epub 2015 Apr 13.**

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Despite increased attention to the evolving nature of war, the unique challenges of contemporary deployment, and women's changing role in warfare, few studies have examined differences in deployment stressors across eras of service or evaluated how gender differences in deployment experiences have changed over time. Using data collected from two national survey studies, we examined war cohort and gender differences in veterans' reports of both mission-related and interpersonal stressors during deployment. Although Operation Enduring Freedom and Operation Iraqi Freedom veterans reported more combat experiences and greater preparedness for deployment compared to Gulf War veterans, Gulf War veterans reported higher levels of other mission-related stressors, including difficult living and working environment, perceived threat, and potential exposure to nuclear, biological, and chemical weapons. Gender differences also emerged, with men reporting greater exposure to mission-related stressors and women reporting higher levels of interpersonal stressors. However, the size and nature of gender differences did not differ significantly when comparing veterans of the two eras. By understanding how risk factors for PTSD differ based on war era and gender, veterans' experiences can be better contextualized.

**Golier JA, Caramanica K, Michaelides AC, Makotkine I, Schmeidler J, Harvey PD, Yehuda R. A randomized, double-blind, placebo-controlled, crossover trial of mifepristone in Gulf War veterans with chronic multisymptom illness. *Psychoneuroendocrinol.* 2016 Feb;64:22-30. doi: 10.1016/j.psyneuen.2015.11.001. Epub 2015 Nov 10.**

No pharmacological treatments have been demonstrated to effectively treat chronic multisymptom illness (CMI) in Gulf War veterans (GWV). This study assessed the effect of the glucocorticoid receptor antagonist mifepristone in GWV with CMI. A randomized, double-blind, cross-over trial of mifepristone, with two six-week treatment phases separated by a one-month washout period, was conducted at a Veterans Affairs (VA) hospital between 2008 and 2011. Participants were randomized to receive either 200mg of mifepristone per day or matched placebo first. The primary clinical outcome measure was change in self-reported physical health. Neurocognitive functioning and self-reported measures of depression, PTSD, and fatigue were secondary outcomes. Sixty-five participants enrolled, of whom 36 were randomized and 32 (mean age, 49.1 (7.2) years) completed the study. Physical and mental health status and neurocognitive functioning were poor at baseline. Mifepristone treatment was not associated with improvement in self-reported physical health ( $p=0.838$ ) or in other self-reported measures of mental health. Mifepristone treatment was significantly associated with improvements in verbal learning ( $p=0.008$ ,  $d=0.508$ ), in the absence of improvement in other cognitive measures (working memory ( $p=0.914$ ), visual learning ( $p=0.643$ ) and a global composite measure ( $p=0.937$ ). Baseline morning cortisol levels and lysozyme IC50-DEX, a measure of peripheral glucocorticoid sensitivity, displayed a significant relationship with endpoint verbal learning scores ( $p=0.012$  and  $p=0.007$ , respectively). The magnitude of cortisol change during treatment mediated the improvement in verbal learning. This study was negative for the primary and secondary clinical outcomes. However, the data suggest a moderate dose of mifepristone may have circumscribed cognitive-enhancing effects in CMI. Further study is warranted to determine whether and through which mechanisms mifepristone treatment

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can yield clinically meaningful improvement in cognitive function in CMI or other neuropsychiatric conditions associated with HPA axis dysregulation.

**Griffiths PD. The first Gulf War and pre-emptive therapy for virology. Rev Med Virol. 2016 May;26(3):144-5. doi: 10.1002/rmv.1882. Epub 2016 Apr 15. Editorial; No abstract available.**

**Gwini SM, Forbes AB, Sim MR, Kelsall HL. Multisymptom Illness in Gulf War Veterans: A Systematic Review and Meta-Analysis. J Occup Environ Med. 2016 Jul;58(7):659-67. doi: 10.1097/JOM.0000000000000755.**

**OBJECTIVE:** The aim of this study was to conduct a systematic review and meta-analysis of multisymptom illness (MSI) in 1990 to 1991 Gulf/Afghanistan/Iraq War veterans. **METHODS:** Electronic databases were searched from January 1990, June 2014 for studies on MSI prevalence in Gulf/Afghanistan/Iraq War veterans, based on the Centers for Disease Control and Prevention MSI case definition, and which included a military comparison group. **RESULTS:** Seven studies were identified among US, UK, and Australian Gulf War veterans; no studies were identified in Afghanistan/Iraq War veterans. MSI prevalence in Gulf War veterans and comparison groups ranged from 26 to 65% and from 12 to 37%, respectively. More recent studies were larger, with improved designs. The pooled odds ratio comparing Gulf War veterans to other military groups was 2.74 (95% confidence interval 2.15 to 3.51). **CONCLUSION:** The systematic review showed that MSI was most prevalent in Gulf War veterans, emphasizing the health burden of MSI in this veteran population.

**Gwini SM, Kelsall HL, Ikin JF, Sim MR, McFarlane AC, Forbes AB. New Onset of Chronic Diseases and Changes in Lifestyle Risk Factors Among Gulf War Veterans: A Longitudinal Comparison of High and Low Symptom Reporters. J Occup Environ Med. 2016 Aug;58(8):770-7. doi: 10.1097/JOM.0000000000000799.**

**OBJECTIVE:** The aim of this study was to compare new chronic diseases onset and longitudinal changes in lifestyle risk factors between Gulf War veterans with different symptom reporting. **METHODS:** Data were collected from Gulf War veterans over two periods, and participants were grouped according to baseline symptom reporting. Logistic, nominal, and ordinal regressions were used for between-group comparisons. **RESULTS:** The veterans comprised low, moderate, and high symptom reporters. New onset of sleep apnea [odds ratio (OR)=9.49; 95% confidence interval (CI)=3.48 to 25.86], musculoskeletal (OR=8.70; 95% CI=4.17 to 18.17), psychological (OR=5.36; 95% CI=2.46 to 11.70), and cardiovascular (OR=3.86; 95% CI=1.33 to 11.23) conditions was elevated in high versus low symptom reporters. Although odds of obesity and alcohol use increased over time and smoking halved, the changes were similar across groups. **CONCLUSIONS:** These findings show increasing obesity and alcohol use, and indicate that high symptomatology among veterans may predict future disease onset.

**Gwini SM, Kelsall HL, Sim MR, Ikin JF, McFarlane AC, Forbes AB. Stability of symptom patterns in Australian Gulf War veterans: 10-year longitudinal study.**

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**Occup Environ Med. 2016 Mar;73(3):195-8. doi: 10.1136/oemed-2015-103169. Epub 2016 Jan 6. Erratum in: Occup Environ Med. 2016 Nov;73(11):804.**

**OBJECTIVES:** Previously we established that symptoms reported by 1990-1991 Gulf War veterans were correlated and exhibited a pattern with 3 factors (psychophysiological distress, somatic distress and arthronemuscular distress), and this pattern was similar to that observed in a military comparison group. In this follow-up study, we examined whether the patterns of symptomatology have changed over time. **METHODS:** Using data on 56 symptoms that was collected in 2000-2003 (wave 1) and 2011-2012 (wave 2) from an Australian cohort of Gulf War veterans (veterans) and a military comparison group, exploratory factor analysis was conducted and Tucker's Congruence Coefficient (TCC) was used to determine factor structure similarity across study groups and waves. **RESULTS:** The results showed that the 3 factors observed at wave 1 were still present at wave 2, and factor structures across study groups and study waves were fairly similar, with TCC ranging 0.86-0.92. Veterans consistently reported more symptoms across all 3 factors. Veterans' symptomatology specific to psychophysiological distress increased between waves 1 and 2 (ratio of means 1.15; 95% CI 1.07 to 1.25) but psychophysiological distress symptomatology was constant in the comparison group (ratio of means 0.97; 95% CI 0.89 to 1.06). Somatic and arthronemuscular distress symptomatology significantly increased over time for both study groups, although at a similar rate. **CONCLUSIONS:** While the symptom groupings (measured by the 3 factors) remained unchanged at 10 years of follow-up, and remained comparable between Gulf War and comparison group, symptomatology continued to be elevated in Gulf War veterans than in the comparison group, and was most evident for psychophysiological distress.

**Ikin JF, McKenzie DP, Gwini SM, Kelsall HL, Creamer M, McFarlane AC, Clarke DM, Wright B, Sim M. Major depression and depressive symptoms in Australian Gulf War veterans 20 years after the Gulf War. J Affect Disord. 2016 Jan 1;189:77-84. doi: 10.1016/j.jad.2015.09.016. Epub 2015 Sep 11.**

**BACKGROUND:** Risk of major depression (depression) was elevated in Australia's Gulf War veterans in a 2000-2002 (baseline) study. A follow up study has measured the Gulf War-related risk factors for depression, also the current prevalence and severity of depression, use of anti-depressant medication, and persistence, remittance or incidence of depression since baseline in Gulf War veterans and a military comparison group. **METHODS:** Participants completed the Composite International Diagnostic Interview v.2.1, the 9-item Patient Health Questionnaire and the Military Service Experience Questionnaire, and consented to Repatriation Pharmaceutical Benefits Scheme (RPBS) and PBS linkage. **RESULTS:** Prevalence of depression (9.7% Gulf War veterans and 7.7% comparison group; adj RR=1.2, 95% CI 0.8-1.7), and pattern of persistence, remittance and incidence of depression since baseline, were similar in the two groups, however veterans reported slightly more severe symptoms (adj median difference 1, 95% CI 0.26-1.74) and were more likely to have been dispensed anti-depressant medication (adj RR=1.56, 95% CI 1.05-2.32). Depression amongst veterans was associated with self-reported Gulf War-related stressors in a dose-response relationship (adj RR 1.06, 95% CI



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1.02-1.09). **LIMITATIONS:** Lower participation rates at follow up resulted in reduced statistical power compared with baseline, Gulf War related stressor data collected at baseline was at risk of recall bias, and RPBS and PBS databases do not capture all dispensed Nervous System medications. **CONCLUSIONS:** More than 20 years after the Gulf War, veterans are experiencing slightly more severe depressive symptoms than a military comparison group, and depression continues to be associated with Gulf War-related stressors.

**Institute of Medicine, National Academies of Sciences, Engineering, and Medicine, Committee on Gulf War and Health, Board on the Health of Select Populations; Cory-Slechta D, Wedge R, editors. Gulf War and Health: Volume 10: Update of Health Effects of Serving in the Gulf War, 2016. Washington (DC): National Academies Press (US); 2016 Mar 16.**

Summary - Sufficient Evidence of a Causal Relationship: Posttraumatic stress disorder (PTSD). Sufficient Evidence of an Association: Generalized anxiety disorder, depression, and substance abuse (particularly alcohol abuse); Gastrointestinal symptoms consistent with functional gastrointestinal disorders such as irritable bowel syndrome and functional dyspepsia; Chronic fatigue syndrome; Gulf War illness. Limited/Suggestive Evidence of an Association: Amyotrophic lateral sclerosis (ALS); Fibromyalgia and chronic widespread pain; Self-reported sexual difficulties. Inadequate/Insufficient Evidence to Determine Whether an Association Exists: Any cancer; Cardiovascular conditions or conditions of the blood and blood-forming organs; Endocrine and metabolic conditions; Neurodegenerative conditions other than ALS; Neurocognitive and neurobehavioral performance; Migraines and other headache disorders; Other neurologic conditions; Respiratory conditions; Structural gastrointestinal conditions; Skin conditions; Musculoskeletal system conditions; Genitourinary conditions; Specific birth defects; Adverse pregnancy outcomes (e.g., miscarriage, stillbirth, preterm birth, and low birth weight); Fertility problems; Increased mortality from any cancer, any neurologic conditions (including multiple sclerosis, Alzheimer's disease, Parkinson's disease, and ALS), respiratory conditions, or gastrointestinal conditions. Limited/Suggestive Evidence of No Association: Objective measures of peripheral neurologic conditions; Multiple sclerosis; Mortality from cardiovascular, infectious, or parasitic diseases; Decreased lung function; Mortality due to mechanical trauma or other external causes.

**James LM, Engdahl BE, Leuthold AC, Georgopoulos AP. Brain Correlates of Human Leukocyte Antigen (HLA) Protection in Gulf War Illness (GWI). EBioMedicine. 2016 Nov;13:72-79. doi: 10.1016/j.ebiom.2016.10.019. Epub 2016 Oct 14.**

Background: We recently reported that six alleles from class II genes of the Human Leukocyte Antigen (HLA) confer protection from Gulf War Illness (GWI) (Georgopoulos et al., 2015). The most significant effect is exerted on Neurological-Cognitive-Mood (NCM), Pain, and Fatigue symptoms, such that higher number of copies of the protective alleles are associated with lower symptom severity. Here we tested the hypothesis that this effect is exerted by modulating the strength of neural synchronicity. Methods: Eighty-one Gulf War veterans (65 with GWI and 16 healthy controls) underwent a

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magnetoencephalography (MEG) scan to assess the strength of brain synchronicity by computing zero-lag crosscorrelations (and their Fisher z transforms) between prewhitened MEG time series. A high-resolution HLA genotyping determined the number of copies,  $k$ , of the 6 protective alleles above in each participant. We tested the hypothesis above by regressing NCM, Pain and Fatigue symptom severity against the interaction term,  $k \times z$  (HLA-related effect), while including  $z$  (non-HLA-related effect), gender and age as covariates. The  $k \times z$  and  $z$  terms assessed HLA- and non-HLA-related effects, respectively, of neural synchronicity on symptom severity. The distributions of these effects in sensor space were visualized using statistical heatmaps. Findings: We found significant, graded HLA- and non-HLA-related effects: (a) NCM > Pain > Fatigue for HLA-related effects, (b) NCM > Fatigue > Pain for non-HLA-related effects, and (c) HLA-related > non-HLA-related effects for all symptoms. These effects had widespread but distinct distributions in sensor space that allowed the orderly separation of the 6 terms (3 symptom domains  $\times$  2 HLA factors) in a multidimensional plot, where one dimension separated the symptoms and the other the HLA relation. Interpretation: These findings demonstrate the presence of substantial, widespread, distinct and orderly HLA- and non-HLA-related neural influences on NCM, Pain and Fatigue symptom severity in GWI.

**Johnson GJ, Slater BC, Leis LA, Rector TS, Bach RR. Blood Biomarkers of Chronic Inflammation in Gulf War Illness. PLoS One. 2016 Jun 28;11(6):e0157855. doi: 10.1371/journal.pone.0157855. eCollection 2016.**

**BACKGROUND:** More than twenty years following the end of the 1990-1991 Gulf War it is estimated that approximately 300,000 veterans of this conflict suffer from an unexplained chronic, multi-system disorder known as Gulf War Illness (GWI). The etiology of GWI may be exposure to chemical toxins, but it remains only partially defined, and its case definition is based only on symptoms. Objective criteria for the diagnosis of GWI are urgently needed for diagnosis and therapeutic research. **OBJECTIVE:** This study was designed to determine if blood biomarkers could provide objective criteria to assist diagnosis of GWI. **DESIGN:** A surveillance study of 85 Gulf War Veteran volunteers identified from the Department of Veterans Affairs Minnesota Gulf War registry was performed. All subjects were deployed to the Gulf War. Fifty seven subjects had GWI defined by CDC criteria, and 28 did not have symptomatic criteria for a diagnosis of GWI. Statistical analyses were performed on peripheral blood counts and assays of 61 plasma proteins using the Mann-Whitney rank sum test to compare biomarker distributions and stepwise logistic regression to formulate a diagnostic model. **RESULTS:** Lymphocyte, monocyte, neutrophil, and platelet counts were higher in GWI subjects. Six serum proteins associated with inflammation were significantly different in GWI subjects. A diagnostic model of three biomarkers-lymphocytes, monocytes, and C reactive protein-had a predicted probability of 90% (CI 76-90%) for diagnosing GWI when the probability of having GWI was above 70%. **SIGNIFICANCE:** The results of the current study indicate that inflammation is a component of the pathobiology of GWI. Analysis of the data resulted in a model utilizing three readily measurable biomarkers that appears to significantly augment the symptom-based case definition of GWI. These new observations are highly relevant to the diagnosis of GWI, and to therapeutic trials.

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**Kearney DJ, Simpson TL, Malte CA, Felleman B, Martinez ME, Hunt SC. Mindfulness-based Stress Reduction in Addition to Usual Care Is Associated with Improvements in Pain, Fatigue, and Cognitive Failures Among Veterans with Gulf War Illness. Am J Med. 2016 Feb;129(2):204-14. doi: 10.1016/j.amjmed.2015.09.015. Epub 2015 Oct 28.**

**BACKGROUND:** Many Gulf War I veterans report ongoing negative health consequences. The constellation of pain, fatigue, and concentration/memory disturbances is referred to as "Gulf War illness." Prior research suggests that mindfulness-based stress reduction may be beneficial for these symptoms, but mindfulness-based stress reduction has not been studied for veterans with Gulf War illness. The objective of this trial was to conduct a pilot study of mindfulness-based stress reduction for veterans with Gulf War illness.

**METHODS:** Veterans (N = 55) with Gulf War illness were randomly assigned to treatment as usual plus mindfulness-based stress reduction or treatment as usual only. Mindfulness-based stress reduction was delivered in 8 weekly 2.5-hour sessions plus a single 7-hour weekend session. Pain, fatigue, and cognitive failures were the primary outcomes, assessed at baseline, after mindfulness-based stress reduction, and 6 months follow-up. Secondary outcomes included symptoms of posttraumatic stress disorder and depression.

**RESULTS:** In intention-to-treat analyses, at 6-month follow-up, veterans randomized to mindfulness-based stress reduction plus treatment as usual reported greater reductions in pain ( $f = 0.33$ ;  $P = .049$ ), fatigue ( $f = 0.32$ ;  $P = .027$ ), and cognitive failures ( $f = 0.40$ ;  $P < .001$ ). Depressive symptoms showed a greater decline after mindfulness-based stress reduction ( $f = 0.22$ ;  $P = .050$ ) and at 6 months ( $f = 0.27$ ;  $P = .031$ ) relative to treatment as usual only. Veterans with posttraumatic stress disorder at baseline randomized to mindfulness-based stress reduction plus treatment as usual experienced significantly greater reductions in symptoms of posttraumatic stress disorder after mindfulness-based stress reduction ( $f = 0.44$ ;  $P = .005$ ) but not at 6 months follow-up ( $f = 0.31$ ;  $P = .082$ ).

**CONCLUSIONS:** Mindfulness-based stress reduction in addition to treatment as usual is associated with significant improvements in self-reported symptoms of Gulf War illness, including pain, fatigue, cognitive failures, and depression.

**Landi A, Broadhurst D, Vernon SD, Tyrrell DL, Houghton M. Reductions in circulating levels of IL-16, IL-7 and VEGF-A in myalgic encephalomyelitis/chronic fatigue syndrome. Cytokine. 2016 Feb;78:27-36. doi: 10.1016/j.cyto.2015.11.018. Epub 2015 Nov 28.**

Recently, differences in the levels of various chemokines and cytokines were reported in patients with myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS) as compared with controls. Moreover, the analyte profile differed between chronic ME/CFS patients of long duration versus patients with disease of less than 3 years. In the current study, we measured the plasma levels of 34 cytokines, chemokines and growth factors in 100 chronic ME/CFS patients of long duration and in 79 gender and age-matched controls. We observed highly significant reductions in the concentration of circulating interleukin (IL)-16, IL-7, and Vascular Endothelial Growth Factor A (VEGF-A) in ME/CFS patients. All three biomarkers were significantly correlated in a multivariate cluster analysis. In addition, we identified significant reductions in the concentrations of fractalkine (CX3CL1) and

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monokine-induced-by-IFN- $\gamma$  (MIG; CXCL9) along with increases in the concentrations of eotaxin 2 (CCL24) in ME/CFS patients. Our data recapitulates previous data from another USA ME/CFS cohort in which circulating levels of IL-7 were reduced. Also, a reduced level of VEGF-A was reported previously in sera of patients with Gulf War Illness as well as in cerebral spinal fluid samples from a different cohort of USA ME/CFS patients. To our knowledge, we are the first to test for levels of IL-16 in ME/CFS patients. In combination with previous data, our work suggests that the clustered reduction of IL-7, IL-16 and VEGF-A may have physiological relevance to ME/CFS disease. This profile is ME/CFS-specific since measurement of the same analytes present in chronic infectious and autoimmune liver diseases, where persistent fatigue is also a major symptom, failed to demonstrate the same changes. Further studies of other ME/CFS and overlapping disease cohorts are warranted in future.

**Li SJ, Flaxman A, Lafta R, Galway L, Takaro TK, Burnham G, Hagopian A. A Novel Method for Verifying War Mortality while Estimating Iraqi Deaths for the Iran-Iraq War through Operation Desert Storm (1980-1993). PLoS One. 2016 Oct 21;11(10):e0164709. doi: 10.1371/journal.pone.0164709. eCollection 2016.**

**OBJECTIVES:** We estimated war-related Iraqi mortality for the period 1980 through 1993. **METHOD:** To test our hypothesis that deaths reported by siblings (even dating back several decades) would correspond with war events, we compared sibling mortality reports with the frequency of independent news reports about violent historic events. We used data from a survey of 4,287 adults in 2000 Iraqi households conducted in 2011. Interviewees reported on the status of their 24,759 siblings. Death rates were applied to population estimates, 1980 to 1993. News report data came from the ProQuest New York Times database. **RESULTS:** About half of sibling-reported deaths across the study period were attributed to direct war-related injuries. The Iran-Iraq war led to nearly 200,000 adult deaths, and the 1990-1991 First Gulf War generated another approximately 40,000 deaths. Deaths during peace intervals before and after each war were significantly lower. We found a relationship between total sibling-reported deaths and the tally of war events across the period,  $p = 0.02$ . **CONCLUSIONS:** We report a novel method to verify the reliability of epidemiological (household survey) estimates of direct war-related injury mortality dating back several decades.

**Maya S, Prakash T, Madhu KD, Goli D. Multifaceted effects of aluminium in neurodegenerative diseases: A review. Biomed Pharmacother. 2016 Oct;83:746-754. doi: 10.1016/j.biopha.2016.07.035. Epub 2016 Jul 29. Review.**

Aluminium (Al) is the most common metal and widely distributed in our environment. Al was first isolated as an element in 1827, and its use began only after 1886. Al is widely used for industrial applications and consumer products. Apart from these it is also used in cooking utensils and in pharmacological agents, including antacids and antiperspirants from which the element usually enters into the human body. Evidence for the neurotoxicity of Al is described in various studies, but still the exact mechanism of Al toxicity is not known. However, the evidence suggests that the Al can potentiate oxidative stress and inflammatory events and finally leads to cell death. Al is considered as a well-established

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neurotoxin and have a link between the exposure and development of neurodegenerative diseases, including Amyotrophic Lateral Sclerosis (ALS), Alzheimer's disease (AD), dementia, Gulf war syndrome and Parkinsonism. Here, we review the detailed possible pathogenesis of AI neurotoxicity. This review summarizes AI induced events likewise oxidative stress, cell mediated toxicity, apoptosis, inflammatory events in the brain, glutamate toxicity, effects on calcium homeostasis, gene expression and AI induced Neurofibrillary tangle (NFT) formation. Apart from these we also discussed animal models that are commonly used for AI induced neurotoxicity and neurodegeneration studies. These models help to find out a better way to treat and prevent the progression in AI induced neurodegenerative diseases.

**McAndrew LM, Helmer DA, Phillips LA, Chandler HK, Ray K, Quigley KS. Iraq and Afghanistan Veterans report symptoms consistent with chronic multisymptom illness one year after deployment. J Rehabil Res Dev. 2016;53(1):59-70. doi: 10.1682/JRRD.2014.10.0255.**

Many Veterans returning from service in Operation Iraqi Freedom/Operation Enduring Freedom (OIF/OEF) experience chronic pain. What is not known is whether for some OIF/OEF Veterans this pain is part of a larger condition of diffuse multisystem symptoms consistent with chronic multisymptom illness (CMI). We use data from a prospective longitudinal study of OIF/OEF Veterans to determine the frequency of CMI. We found that 1 yr after deployment, 49.5% of OIF/OEF Veterans met criteria for mild to moderate CMI and 10.8% met criteria for severe CMI. Over 90% of Veterans with chronic pain met criteria for CMI. CMI was not completely accounted for either by posttraumatic stress disorder or by predeployment levels of physical symptoms. Veterans with symptoms consistent with CMI reported significantly worse physical health function than Veterans who did not report symptoms consistent with CMI. This study suggests that the presence of CMI should be considered in the evaluation of OIF/OEF Veterans. Further, it suggests the pain management for these Veterans may need to be tailored to take CMI into consideration.

**Naeser MA, Martin PI, Ho MD, Krengel MH, Bogdanova Y, Knight JA, Yee MK, Zafonte R, Frazier J, Hamblin MR, Koo BB. Transcranial, Red/Near-Infrared Light-Emitting Diode Therapy to Improve Cognition in Chronic Traumatic Brain Injury. Photomed Laser Surg. 2016 Dec;34(12):610-626. doi: 10.1089/pho.2015.4037. Review.**

We review the general topic of traumatic brain injury (TBI) and our research utilizing transcranial photobiomodulation (tPBM) to improve cognition in chronic TBI using red/near-infrared (NIR) light-emitting diodes (LEDs) to deliver light to the head. tPBM improves mitochondrial function increasing oxygen consumption, production of adenosine triphosphate (ATP), and improving cellular energy stores. Nitric oxide is released from the cells increasing regional blood flow in the brain. Review of published studies: In our previously published study, 11 chronic TBI patients with closed-head TBI caused by different accidents (motor vehicle accident, sports-related, improvised explosive device blast injury) and exhibiting long-lasting cognitive dysfunction received 18 outpatient treatments (Monday, Wednesday, Friday for 6 weeks) starting at 10 months to 8 years

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post-TBI. LED therapy is nonthermal, painless, and noninvasive. An LED-based device classified as nonsignificant risk (FDA cleared) was used. Each LED cluster head (5.35 cm diameter, 500 mW, 22.2 mW/cm<sup>2</sup>) was applied for 9 min 45 sec (13 J/cm<sup>2</sup>) using 11 locations on the scalp: midline from front-to-back hairline and bilaterally on frontal, parietal, and temporal areas. Testing was performed before and after transcranial LED (tLED; at 1 week, 1 month, and at 2 months after the 18th treatment) and showed significant improvements in executive function and verbal memory. There were also fewer post-traumatic stress disorder (PTSD) symptoms reported. Ongoing studies: Ongoing, current studies involve TBI patients who have been treated with tLED using either 26 J/cm<sup>2</sup> per LED location on the head or treated with intranasal only (iLED) using red (633 nm) and NIR (810 nm) diodes placed into the nostrils. The NIR iLED is hypothesized to deliver photons to the hippocampus, and the red 633 nm iLED is believed to increase melatonin. Results have been similar to the previously published tLED study. Actigraphy sleep data showed increased time asleep (on average one additional hour per night) after the 18th tLED or iLED treatment. LED treatments may be performed in the home. Sham-controlled studies with veterans who have cognitive dysfunction from Gulf War Illness, blast TBI, and TBI/PTSD are currently ongoing.

**Nissen LR, Stoltenberg C, Nielsen AB, Vedtofte MS, Marott JL, Gyntelberg F, Guldager B. Danish Gulf War Veterans Revisited: No Evidence of Increased Sickness Absence or Reduced Labor Market Outcome After Deployment to the Persian Gulf. *Mil Med.* 2016 Nov;181(11):e1644-e1649.**

**OBJECTIVE:** To examine the assumption that postdeployment incidence of sickness and other absence from work are higher among Gulf War Veterans compared with nonveterans. **METHODS:** A prospective registry study including a cohort of 721 Danish Gulf War Veterans and a control cohort of 3,629 nonveterans selected from the general Danish population. Outcome measures were up to 23 years postdeployment incidence of (1) long-term sickness absence and (2) long-term all types of absence from work. Long term with regard to sickness and other absence was defined as exceeding 8 weeks. The association between outcomes and information on deployment history was studied using time-to-event analysis. The index date was the return date from the last deployment to the Gulf. The follow-up period was the time from index date until April 27, 2014. **RESULTS:** As the main finding, no difference was found between veterans and nonveterans in the incidence rate of long-term sickness absence. After an initial short period (3 months) with elevated incidence rate of long-term absence from work among veterans, there was no difference between the cohorts. **CONCLUSION:** Among Danish Gulf War Veterans, no postdeployment increased risk of long-term sickness absence or long-term absence from work was found as compared with nonveterans.

**O'Callaghan JP, Michalovicz LT, Kelly KA. Supporting a Neuroimmune Basis of Gulf War Illness. *EBioMedicine.* 2016 Nov;13:5-6. doi: 10.1016/j.ebiom.2016.10.037. Epub 2016 Oct 26. Commentary; No abstract available.**

**Phillips KF, Deshpande LS. Repeated low-dose organophosphate DFP exposure leads to the development of depression and cognitive impairment in a rat model of**

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**Gulf War Illness. *Neurotoxicol.* 2016 Jan;52:127-33. doi: 10.1016/j.neuro.2015.11.014. Epub 2015 Nov 24.**

Approximately 175,000-250,000 of the returning veterans from the 1991 Persian Gulf War exhibit chronic multi-symptom illnesses that includes neurologic co-morbidities such as depression, anxiety and cognitive impairments. Amongst a host of causative factors, exposure to low levels of the nerve agent Sarin has been strongly implicated for expression of Gulf War Illness (GWI). Nerve agents similar to pesticides are organophosphate (OP) compounds. There is evidence from civilian population that exposure to OPs such as in agricultural workers and nerve agents such as the survivors and first-responders of the Tokyo subway Sarin gas attack suffer from chronic neurological problems similar to GWI symptoms. Given this unique chemical profile, OPs are ideal to study the effects of nerve agents and develop models of GWI in civilian laboratories. In this study, we used repeated low-dose exposure to OP agent diisopropyl fluorophosphate (DFP) over a 5-day period to approximate the duration and level of Sarin exposure during the Persian Gulf War. We tested the rats at 3-months post DFP exposure. Using a battery of behavioral assays, we observed the presence of symptoms of chronic depression, anxiety and memory problems as characterized by increased immobility time in the Forced Swim Test, anhedonia in the Sucrose Preference Test, anxiety in the Elevated Plus Maze, and spatial memory impairments in the Object Location Test, respectively. Chronic low dose DFP exposure was also associated with hippocampal neuronal damage as characterized by the presence of Fluoro-Jade staining. Given that OP exposure is considered a leading cause of GWI related morbidities, this animal model will be ideally suited to study underlying molecular mechanisms for the expression of GWI neurological symptoms and identify drugs for the effective treatment of GWIs.

**Pierce LM, Kurata WE, Matsumoto KW, Clark ME, Farmer DM. Long-term epigenetic alterations in a rat model of Gulf War Illness. *Neurotoxicology.* 2016 Jul;55:20-32. doi: 10.1016/j.neuro.2016.05.007. Epub 2016 May 11.**

Gulf War Illness (GWI) is a chronic, multisymptom illness that affects 25% of the 700,000 US veterans deployed to the Persian Gulf during the 1990-1991 Gulf War. Central nervous system impairments are among the most common symptoms reported, including memory dysfunction and depression. After 25 years, the diagnosis remains elusive, useful treatments are lacking, and the cause is poorly understood, although exposures to pyridostigmine bromide (PB) and pesticides are consistently identified to be among the strongest risk factors. Epigenetic changes including altered microRNA (miRNA) expression and DNA methylation play an important role in learning, memory, and emotion regulation and have been implicated in various neurological disorders. In this study, we used an established rat model of GWI to determine whether 1) chronic alterations in miRNA expression and global DNA methylation and DNA hydroxymethylation are mechanisms involved in the pathobiology of GWI, and 2) plasma exosome small RNAs may serve as potential noninvasive biomarkers of this debilitating disease. One year after a 28-day exposure regimen of PB, DEET (N,N-diethyl-3-methylbenzamide), permethrin, and mild stress, expression of 84 mature miRNAs and global 5-methylcytosine (5mC) and 5-hydroxymethylcytosine (5hmC) content were analyzed in the brains of GWI rats and

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vehicle controls by PCR array and enzyme-linked immunosorbent assay, respectively. Plasma exosome RNA next-generation sequencing analysis was performed in pooled samples to discover potential noninvasive biomarkers. We found that combined exposure to low doses of GW-related chemicals and mild stress caused epigenetic modifications in the brain that persisted one year after exposure, including increased expression of miR-124-3p and miR-29b-3p in the hippocampus and regional alterations in global 5mC and 5hmC content. GW-relevant exposures also induced the differential expression of two piwi-interacting RNAs (piRNAs) in circulation (piR-007899 and piR-019162). Results from this study implicate a role for epigenetic alterations in GWI. Evaluation of the diagnostic potential of plasma exosome RNAs in veterans with GWI is warranted.

**Repine JE, Wilson P, Elkins N, Klawitter J, Christians U, Peters B, Smith DM. Inhalation of two putative Gulf War toxins by mice. J Environ Sci Health B. 2016;51(6):366-73. doi: 10.1080/03601234.2016.1142318. Epub 2016 Mar 7. Erratum in: J Environ Sci Health B. 2016 Sep;51(9):654.**

We employed our inhalation methodology to examine whether biomarkers of inflammation and oxidative stress would be produced in mice following inhalation of aerosols containing carbonaceous particles or the vapor of pesticides prevalent during the first Gulf War. Exposure to two putative Gulf War Illness toxins, fine airborne particles and the pesticide malathion, increased biomarkers of inflammation and oxidative stress in Friend virus B (FVB) female mice. Mice inhaling particles 24 h before had increased lung lavage and plasma Leukotriene B4 (LTB4) (a biomarker of inflammation) and PGF2 $\alpha$  (a biomarker of oxidative stress) levels, lung lavage protein and lung lavage lactic dehydrogenase (LDH) levels. These changes were a function of particle density and exposure time. Compared to particle inhalation, mice inhaling malathion 24 h before had small increase in plasma LTB4 and PGF2 $\alpha$  levels but no increase in lung lavage LTB4, lung lavage protein, lung lavage LDH, and lung lavage alveolar macrophage (AM) levels compared to unexposed control mice. AM from particle-exposed mice contained phagocytosed particles, while AM from malathion-exposed mice showed no abnormalities. Our results indicate that inhaling particles or malathion can alter inflammatory and oxidative biomarkers in mice and raise the possibility that these toxins may have altered inflammation and oxidative stress biomarkers in Gulf War-exposed individuals.

**Rice M, Craddock T, Folcik V, del Rosario R, Barnes Z, Klimas N, Fletcher M, Zysman J, Broderick G. Gulf War Illness: is There Lasting Damage to Endocrine-immune Circuitry? Systems Biomedicine. 2016; (2):80-89.**

We reported previously that the persistence of complex immune, endocrine and neurological symptoms that afflict up to one third of veterans from the 1990-91 Gulf War might be supported by a misdirected regulatory drive. Here we use a detailed model of immune signaling in concert with an overarching circuit model of known sex and stress hormone co-regulation to explore how the failure of regulatory elements may further establish a self-perpetuating imbalance that closely resembles Gulf War Illness (GWI). Defects to the model were imparted iteratively and the stable regulatory modes supported by these altered immune-endocrine circuits were identified using repeated simulation



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experiments. In each case the predicted homeostatic regimes were compared to experimental data collected in male GWI (n=20 ) and matched healthy veterans (n=22 ). We found that alignment of GWI with a new homeostatic regime improved significantly when cortisol's normal anti-inflammatory activity was interrupted. Alignment improved further when this cortisol insensitivity was compounded by the loss of the normal antagonistic effects of Th1 cytokines on Th2 lymphocyte activation. Together these simulation results suggest altered glucocorticoid gene regulation compounded by possible changes in IGF-1 regulation of Th1:Th2 immune balance may be key underlying features of GWI.

**Spencer PS, Palmer VS, Kisby GE. Seeking environmental causes of neurodegenerative disease and envisioning primary prevention. *Neurotoxicology*. 2016 Sep;56:269-283. doi: 10.1016/j.neuro.2016.03.017. Epub 2016 Apr 2.**

Pathological changes of the aging brain are expressed in a range of neurodegenerative disorders that will impact increasing numbers of people across the globe. Research on the causes of these disorders has focused heavily on genetics, and strategies for prevention envision drug-induced slowing or arresting disease advance before its clinical appearance. We discuss a strategic shift that seeks to identify the environmental causes or contributions to neurodegeneration, and the vision of primary disease prevention by removing or controlling exposure to culpable agents. The plausibility of this approach is illustrated by the prototypical neurodegenerative disease amyotrophic lateral sclerosis and parkinsonism-dementia complex (ALS-PDC). This often-familial long-latency disease, once thought to be an inherited genetic disorder but now known to have a predominant or exclusive environmental origin, is in the process of disappearing from the three heavily affected populations, namely Chamorros of Guam and Rota, Japanese residents of Kii Peninsula, Honshu, and Auyu and Jaqai linguistic groups on the island of New Guinea in West Papua, Indonesia. Exposure via traditional food and/or medicine (the only common exposure in all three geographic isolates) to one or more neurotoxins in seed of cycad plants is the most plausible if yet unproven etiology. Neurotoxin dosage and/or subject age at exposure might explain the stratified epidemic of neurodegenerative disease on Guam in which high-incidence ALS peaked and declined before that of PD, only to be replaced today by a dementing disorder comparable to Alzheimer's disease. Exposure to the Guam environment is also linked to the delayed development of ALS among a subset of Chamorro and non-Chamorro Gulf War/Era veterans, a summary of which is reported here for the first time. Lessons learned from this study and from 65 years of research on ALS-PDC include the exceptional value of initial, field-based informal investigation of disease-affected individuals and communities, the results of which can provide an invaluable guide to steer cogent epidemiological and laboratory-based research.

**Sripada RK, Lamp KE, Defever M, Venners M, Rauch SA. Perceived Social Support in Multi-era Veterans With Posttraumatic Stress Disorder. *J Nerv Ment Dis*. 2016 Apr;204(4):317-20. doi: 10.1097/NMD.0000000000000476.**

Low social support is associated with greater prevalence and severity of posttraumatic stress disorder (PTSD). However, the factors that explain the association between social

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support and PTSD are not well understood. In the current study, 741 VA patients who presented to a PTSD clinic between 2005 and 2013 completed assessments of symptom severity and social support. Analysis of variance and linear regression tested the associations between social support, sociodemographic characteristics, and PTSD symptom severity. In adjusted analyses, social support was robustly associated with PTSD severity ( $\beta = -0.30$ ,  $p < 0.001$ ). After stratification by combat era, this association remained significant for all era veterans except veterans of the post-Vietnam/Desert Storm era. Other sociodemographic characteristics did not affect the association between social support and PTSD. Our findings suggest that the detrimental effects of poor social support pervade across sociodemographic groups and that efforts to improve social support in veterans with PTSD are needed.

**Turner MP, Hubbard NA, Himes LM, Faghihahmadabadi S, Hutchison JL, Bennett IJ, Motes MA, Haley RW, Rypma B. Cognitive Slowing in Gulf War Illness Predicts Executive Network Hyperconnectivity: Study in a Population-Representative Sample. *Neuroimage Clin.* 2016 Aug 26;12:535-541. eCollection 2016.**

Cognitive slowing is a prevalent symptom observed in Gulf War Illness (GWI). The present study assessed the extent to which functional connectivity between dorsolateral prefrontal cortex (DLPFC) and other task-relevant brain regions was predictive of GWI-related cognitive slowing. GWI patients ( $n = 54$ ) and healthy veteran controls ( $n = 29$ ) were assessed on performance of a processing speed task (the Digit Symbol Substitution Task; DSST) while undergoing functional magnetic resonance imaging (fMRI). GWI patients were slower on the DSST relative to controls. Bilateral DLPFC connectivity with task-relevant nodes was altered in GWI patients compared to healthy controls during DSST performance. Moreover, hyperconnectivity in these networks predicted GWI-related increases in reaction time on the DSST, whereas hypoconnectivity did not. These results suggest that GWI-related cognitive slowing reflects reduced efficiency in cortical networks.

**White RF, Steele L, O'Callaghan JP, Sullivan K, Binns JH, Golomb BA, Bloom FE, Bunker JA, Crawford F, Graves JC, Hardie A, Klimas N, Knox M, Meggs WJ, Melling J, Philbert MA, Grashow R. Recent research on Gulf War illness and other health problems in veterans of the 1991 Gulf War: Effects of toxicant exposures during deployment. *Cortex.* 2016 Jan;74:449-75. doi: 10.1016/j.cortex.2015.08.022. Epub 2015 Sep 25. Review.**

Veterans of Operation Desert Storm/Desert Shield - the 1991 Gulf War (GW) - are a unique population who returned from theater with multiple health complaints and disorders. Studies in the U.S. and elsewhere have consistently concluded that approximately 25-32% of this population suffers from a disorder characterized by symptoms that vary somewhat among individuals and include fatigue, headaches, cognitive dysfunction, musculoskeletal pain, and respiratory, gastrointestinal and dermatologic complaints. Gulf War illness (GWI) is the term used to describe this disorder. In addition, brain cancer occurs at increased rates in subgroups of GW veterans, as do neuropsychological and brain imaging abnormalities. Chemical exposures have become the focus of etiologic GWI research because nervous system symptoms are prominent and many neurotoxicants were present

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in theater, including organophosphates (OPs), carbamates, and other pesticides; sarin/cyclosarin nerve agents, and pyridostigmine bromide (PB) medications used as prophylaxis against chemical warfare attacks. Psychiatric etiologies have been ruled out. This paper reviews the recent literature on the health of 1991 GW veterans, focusing particularly on the central nervous system and on effects of toxicant exposures. In addition, it emphasizes research published since 2008, following on an exhaustive review that was published in that year that summarizes the prior literature (RACGWI, 2008). We conclude that exposure to pesticides and/or to PB are causally associated with GWI and the neurological dysfunction in GW veterans. Exposure to sarin and cyclosarin and to oil well fire emissions are also associated with neurologically based health effects, though their contribution to development of the disorder known as GWI is less clear. Gene-environment interactions are likely to have contributed to development of GWI in deployed veterans. The health consequences of chemical exposures in the GW and other conflicts have been called "toxic wounds" by veterans. This type of injury requires further study and concentrated treatment research efforts that may also benefit other occupational groups with similar exposure-related illnesses.

**Yee MK, Seichepine DR, Janulewicz PA, Sullivan KA, Proctor SP, Kregel MH. Self-Reported Traumatic Brain Injury, Health and Rate of Chronic Multisymptom Illness in Veterans From the 1990-1991 Gulf War. J Head Trauma Rehabil. 2016 Sep-Oct;31(5):320-8. doi: 10.1097/HTR.000000000000173.**

**BACKGROUND:** Traumatic brain injury (TBI) was not considered to be common in the 1990-1991 Gulf War (GW). Therefore, the relationship between TBI and chronic health symptoms experienced by GW veterans is unknown. Health symptoms reported by veterans deployed more recently to this region (Operations Enduring and Iraqi Freedom) are similar to those of GW veterans and have been primarily attributed to TBI.

**OBJECTIVE:** To examine the relationships among self-reported TBI, health symptoms, chronic multisymptom illness (CMI), and health-related quality of life among GW veterans. **PARTICIPANTS:** Participants included 1 274 GW veterans from the Devens Cohort Study, 156 of whom self-reported a history of TBI (12.2% of the sample). **DESIGN:** Cross-sectional retrospective analysis of existing survey data. **MAIN MEASURES:** A 52-item health symptom checklist and the RAND 36-Item Health short Form Survey. **RESULTS:** Self-reported TBI in GW Veterans is related to increased rates of health symptoms, CMI, and poorer health-related quality of life. **CONCLUSIONS:** Gulf War veterans' self-reported exposure to TBI is related to increased rates of chronic health symptoms and CMI, which interfere with everyday activities of daily living.

**Zakirova Z, Crynen G, Hassan S, Abdullah L, Horne L, Mathura V, Crawford F, Ait-Ghezala G. A Chronic Longitudinal Characterization of Neurobehavioral and Neuropathological Cognitive Impairment in a Mouse Model of Gulf War Agent Exposure. Front Integr Neurosci. 2016 Jan 12;9:71. doi: 10.3389/fnint.2015.00071. eCollection 2015.**

Gulf War Illness (GWI) is a chronic multisymptom illness with a central nervous system component that includes memory impairment as well as neurological and musculoskeletal

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deficits. Previous studies have shown that in the First Persian Gulf War conflict (1990–1991) exposure to Gulf War (GW) agents, such as pyridostigmine bromide (PB) and permethrin (PER), were key contributors to the etiology of GWI. For this study, we used our previously established mouse model of GW agent exposure (10 days PB+PER) and undertook an extensive lifelong neurobehavioral characterization of the mice from 11 days to 22.5 months post exposure in order to address the persistence and chronicity of effects suffered by the current GWI patient population, 24 years post-exposure. Mice were evaluated using a battery of neurobehavioral testing paradigms, including Open Field Test (OFT), Elevated Plus Maze (EPM), Three Chamber Testing, Radial Arm Water Maze (RAWM), and Barnes Maze (BM) Test. We also carried out neuropathological analyses at 22.5 months post exposure to GW agents after the final behavioral testing. Our results demonstrate that PB+PER exposed mice exhibit neurobehavioral deficits beginning at the 13 months post exposure time point and continuing trends through the 22.5 month post exposure time point. Furthermore, neuropathological changes, including an increase in GFAP staining in the cerebral cortices of exposed mice, were noted 22.5 months post exposure. Thus, the persistent neuroinflammation evident in our model presents a platform with which to identify novel biological pathways, correlating with emergent outcomes that may be amenable to therapeutic targeting. Furthermore, in this work we confirmed our previous findings that GW agent exposure causes neuropathological changes, and have presented novel data which demonstrate increased disinhibition, and lack of social preference in PB+PER exposed mice at 13 months after exposure. We also extended upon our previous work to cover the lifespan of the laboratory mouse using a battery of neurobehavioral techniques.

#### **IV. RESEARCH FUNDING TRENDS**

This section provides a quantitative overview of the current research portfolio on GWVI and the evolution of the portfolio since 2007. Topics that are covered include research expenditures by VA, DoD, and HHS from FY 2007-2016, and the number of research projects in which the Federal Government has invested.

The appropriated funds for FY 2007 through 2016, centrally obligated to each project, are shown in Appendix C and summarized in Table IV-1. Federal funding for GW research totaled almost \$280 million during this period. Funds obligated for these projects prior to FY 2007 are not shown in either Table IV-1 or Appendix C. Since many projects are multi-year efforts for which funds are obligated at the beginning of the project period, projects that received all of their funds prior to FY 2007 are listed with no associated obligation (\$0) in Appendix C. Federal funds for these earlier projects were reported in prior annual reports.

**Table IV-1. 10-Year (FY 2007-2016) Funding Trends for GW Research in Millions of Dollars**

Department	FY '07	FY '08	FY '09	FY '10	FY '11	FY '12	FY '13	FY '14	FY '15	FY '16	Total Costs FY '07-'16
<b>DoD</b>	\$ 3.4	\$ 11.7	\$ 10.4	\$ 10.4	\$ 10.3	\$ 11.7	\$ 19.5	\$ 22.5	\$ 23.8	\$ 24.3	<b>\$ 148.0</b>
<b>HHS</b>	\$ 0.5	\$ 0.4	\$ 0	\$ 0	\$ 0	\$ 0	\$ 0	\$ 0	\$ 0	\$ 0	<b>\$ 0.9</b>
<b>VA</b>	\$ 22.1	\$ 21.9	\$ 16.6	\$13.9	\$ 5.6	\$ 6.7	\$ 7.9	\$ 9.7	\$ 11.6	\$ 12.4	<b>\$ 128.4</b>
<b>Total</b>	<b>\$ 26.0</b>	<b>\$ 34.0</b>	<b>\$ 27.0</b>	<b>\$ 24.3</b>	<b>\$ 15.9</b>	<b>\$ 18.4</b>	<b>\$ 27.4</b>	<b>\$ 32.2</b>	<b>\$ 35.4</b>	<b>\$ 36.6</b>	<b>\$ 277.3</b>

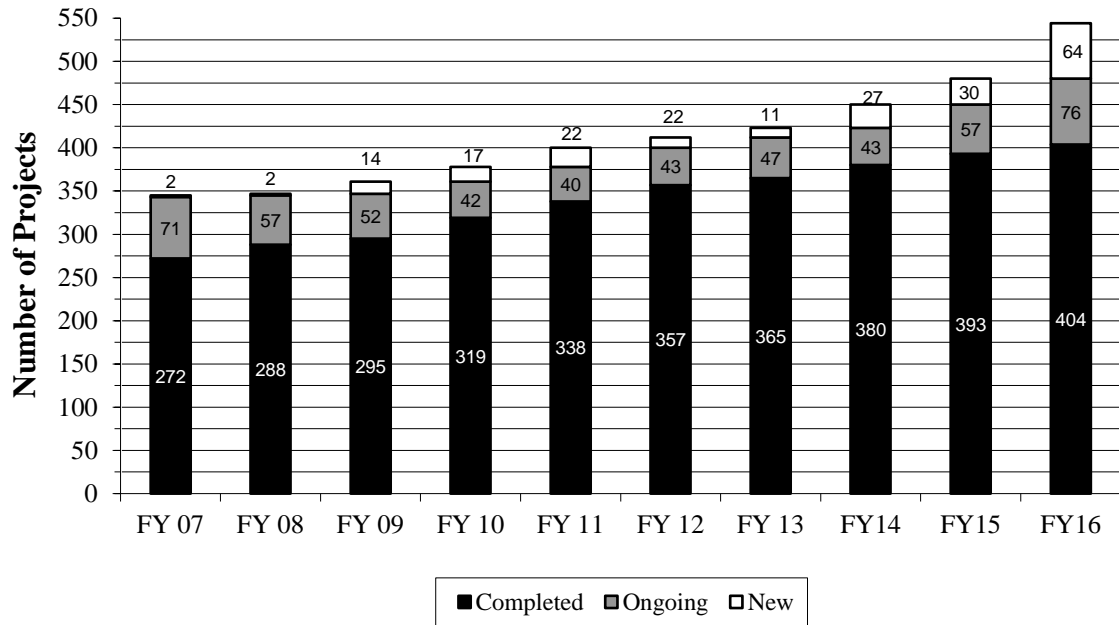
The funding level for FY 2015 in the table above differs from the value reported in the 2015 Annual Summary due to the delayed start of 28 projects funded through the FY 2015 appropriation for the Gulf War Illness Research (GWIRP) managed by the Congressionally Directed Medical Research Programs (CDMRP) at DoD. DoD did not receive final approval until after the 2015 Annual Summary was prepared.

VA, DoD, and HHS sponsored a total of 544 distinct research projects on GWVI during the period of FY 1992 through FY 2016. Appendix A lists all of the research and development projects and programs supported now or in the past by each of the three Federal agencies. Nine projects have been dual-funded by VA and DoD, and each agency has given the project its own unique project number (DoD-115/VA-062; DoD-116/VA-063; DoD-116A/VA-063A; DoD-116B/VA-063B; DoD-118/VA-061; DoD-119/VA-055; DoD-125/VA-074; DoD-143/VA-078; and DoD-154/VA-088). In prior annual reports to Congress, the total number of funded projects was corrected for the number of dual-funded projects. Starting with the 2005 annual report to Congress, this practice has been discontinued since VA and DoD may start or end funding of their portion of these projects independent of each other. Any dual-funded project would, therefore, be treated as two distinct projects.

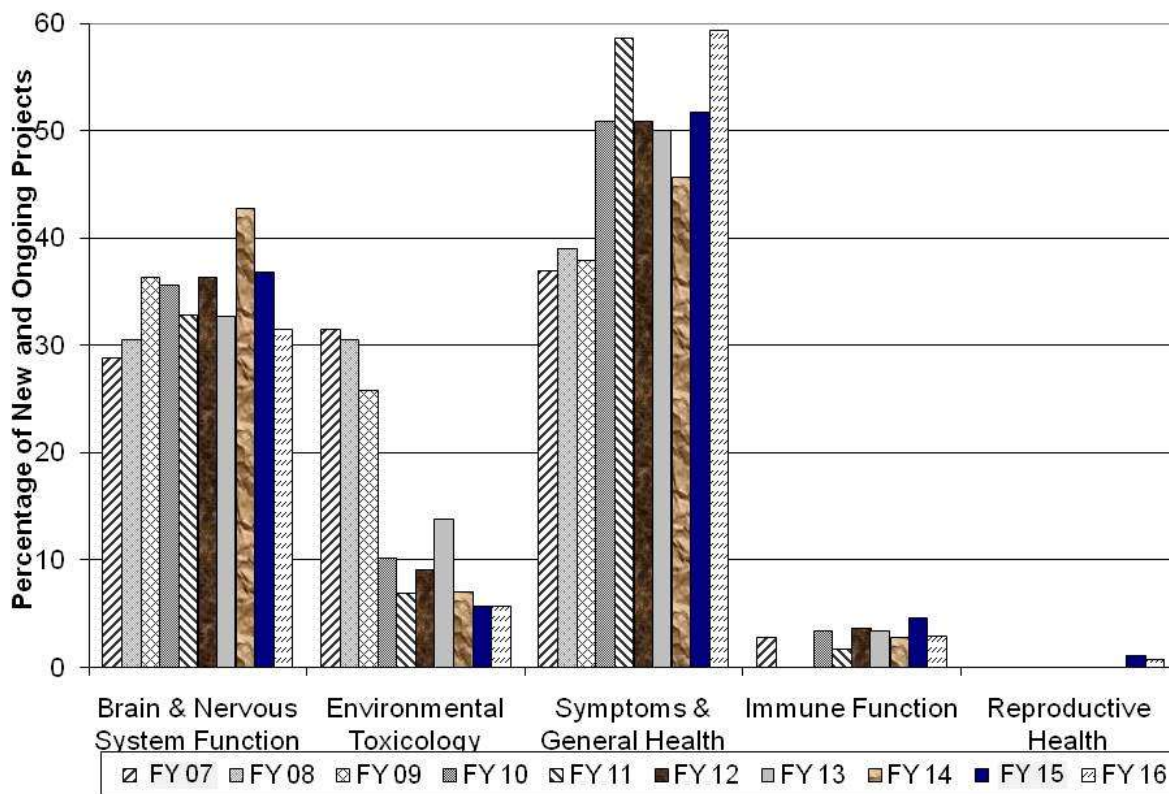
The numbers of new, ongoing, and completed projects for FY 2007 - FY 2016 are shown in Figure IV-1. As of September 30, 2016, 404 projects (74 percent of the 544 projects) were completed, and 140 projects (26 percent) were new or ongoing.

The annual distribution of new and ongoing projects within the five major Research Focus Areas is shown in Figure IV-2.

**Figure IV-1. Cumulative Number of Funded Projects (FY 2007 - FY 2016)**



**Figure IV-2. Annual Distribution of Topic Areas for New and Ongoing Projects**



## V. NEW RESEARCH PROJECTS AND INITIATIVES

### A. New Initiatives

Program Announcements (PAs) and Requests for Applications (RFAs) were issued by CDMRP and VA in FY 2016. Proposals received for review in response to these PAs and RFAs were reviewed, and projects selected for funding will begin in FY 2017. As more investigators engage in GW research, there has been an increase in applications for funding and increases in the number of newly-approved treatment trials and biomarker studies. In 2016, 36 newly awarded projects were added to the 76 ongoing projects and 28 additional projects were selected for funding.

In addition to the RFAs for Biomedical Laboratory Research & Development and Clinical Sciences R&D, a VA RFA in Health Services R&D asked researchers to propose ways of determining if GW Veterans are satisfied with their health care at VA and to propose solutions to any problems they identify. Thus far, five projects have been recommended for funding.

Two CDMRP-funded research consortia combine the talents and expertise of GW researchers who focus on different aspects of GWI. One consortium studies brain-immune interactions to monitor neurotoxic and neuroinflammatory reactions as the investigators try

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to understand the underlying causes of the health problems in GW Veterans. The other consortium is focused on a “systems biology” approach to combining basic research with clinical results to identify biomarkers and possible treatments for GW Veterans.

The National Academy of Medicine (NAM; formerly the Institute of Medicine) released a study for VA entitled “Gulf War and Health, Volume 10: Update of Health Effects of Serving in the Gulf War, 2016” on February 11, 2016. A follow-up study, “Gulf War and Health, Volume 11: Generational Health Effects of Serving in the Gulf War,” was contracted by VA in 2016 with an expected completion date in 2018. An NAM report entitled “Evaluation of the Congressionally Directed Medically Research Programs Review Process” and released on November 15, 2016, was requested by the Defense Health Agency (DHA) to evaluate the review process and to determine the extent of coordination between CDMRP and other agencies like NIH and VA. The CDMRP Gulf War program was part of this NAM review.

## **B. Portfolio Review**

VA and DoD each review their portfolios of GW research on a regular basis in order to determine research gaps and to expand successful research topic areas. The Federal GW research portfolio is increasingly focused on identifying potential new treatments (clinical trials, including complementary medicine approaches) for ill GW Veterans and identifying new diagnostic markers of disease and potential therapeutic targets to develop new therapies. VA and DoD program managers meet regularly to share information regarding funded GW research projects and coordinate activities, whenever possible, to maximize combined program impact. To formalize this process, the GW research programs have been integrated into the ongoing Department-wide VA-DoD Review and Analysis meetings. The third such GW review was held in September 2017, and the next review will be in 2018.

## **C. New Projects**

This section highlights the new research projects that have been approved since last year’s 2015 Annual Summary; these projects represent an investment of more than \$30 million by the time they are completed. They are described below and incorporated into the tables in Appendices A, B, and C.

### **DoD Projects**

Fifty-six new projects were recommended for funding through the FY 2016 appropriation or in CY 2015 after the previous annual summary was submitted for the GWIRP managed by CDMRP. These projects focused on Brain and Nervous System Function (13), Environmental Toxicology (4), Symptoms and General Health (38), and Immune Function (1).

\*DoD-269, “The Role of Desert-Dust Metals in the Pathobiology of Gulf War Illness” is designed to determine if exposure to pyridostigmine bromide (PB), permethrin (PM), or



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DEET, followed by exposure to metals shown to be associated with desert dust, results in an ability of those metals to cross the blood-brain barrier. An in vitro model that mimics the blood-brain barrier will be used for these studies. If PB, PM, or DEET exposure results in metals crossing the blood-brain barrier, it suggests that a previously uninvestigated multi-exposure scenario may play a role in the manifestation of Gulf War illness.

\*DoD-270, "Examination of Plasma PON1 Paraoxonase Activity and Genotype in Gulf War Veterans" will investigate the extent to which genetic variability in PON1, specifically the ability of PON1 to neutralize different types of organophosphates (OPs), and GW Veterans' exposure to those OPs contribute to their risk for developing GWI. A model that explains why certain GW Veterans developed GWI while others with similar deployment experiences and exposures remained healthy will be tested using a large (> 800) sample of existing/ongoing GW cohorts.

\*DoD-271, "Neuroepidemiologic Case Definition of Gulf War Illness from Neuroimaging and EEG in a Population-Representative Nested Case-Control Sample of Gulf War Veterans" will continue to develop a population-representative comparative epidemiologic description of the rates of GWI symptomatology and clinical diagnoses in an established cohort of deployed and non-deployed GW veterans.

\*DoD-272, "Examination of Neuroimaging, Cognitive Functioning, and Plasma Biomarkers in a Longitudinal Cohort: Fort Devens" is designed to improve understanding of the pathobiology for the chronicity of symptoms in GWI. The goal is to develop brain imaging and peripheral blood plasma biomarkers of oxidative stress that correlate with cognitive and health symptom outcomes in a well-established GWV cohort.

\*DoD-273 Partnered award to DoD-272, "Examination of Neuroimaging, Cognitive Functioning, and Plasma Markers in a Longitudinal Cohort of Gulf War Deployed Veterans: The Fort Devens Cohort" is designed to improve understanding of the pathobiology for the chronicity of symptoms in GWI. The goal is to develop brain imaging and peripheral blood plasma biomarkers of oxidative stress that correlate with cognitive and health symptom outcomes in a well-established GWV cohort.

\*DoD-274, "Stress Hormone Enhancement of OP-Induced Neuroinflammation as an Animal Model of GWI: The Role of Toll-Like Receptors and Plasticity" will build on prior findings related to the effect of physiological stressors and exposure to irreversible organophosphate (OP) cholinesterase inhibitors as a basis for developing GWI, and extend key findings with diisopropyl fluorophosphate (DFP) to the additional GWI-relevant OPs, chlorpyrifos (CPF), and dichlorvos (DDVP). Also, a greater understanding of the basis of the corticosterone (CORT) "priming" effect is needed to identify targets for therapeutic intervention. Toll-like receptor 2 (TLR2) pathways in the signaling underlying neuroinflammatory "priming" have been implicated, and the role of TLR2 in the development of CORT-OP-induced neuroinflammation will be investigated. This study will also define the extended duration of the synaptic and behavioral effects resulting from CORT and OP-induced neuroinflammation and attempt to diminish this condition with pharmacological trophic factors that affect neurogenesis and plasticity.

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\*DoD-275 Partnered award to DoD-274, “Stress Hormone Enhancement of OP-Induced Neuroinflammation as an Animal Model of GWI: The Role of Toll-Like Receptors and Plasticity” will build on prior findings related to the effect of physiological stressors and exposure to irreversible organophosphate (OP) cholinesterase inhibitors as a basis for developing GWI, and extend key findings with diisopropyl fluorophosphate (DFP) to the additional GWI-relevant OPs, chlorpyrifos (CPF), and dichlorvos (DDVP). Also, a greater understanding of the basis of the corticosterone (CORT) "priming" effect is needed to identify targets for therapeutic intervention. Toll-like receptor 2 (TLR2) pathways in the signaling underlying neuroinflammatory "priming" have been implicated, and the role of TLR2 in the development of CORT-OP-induced neuroinflammation will be investigated. This study will also define the extended duration of the synaptic and behavioral effects resulting from CORT and OP-induced neuroinflammation and attempt to diminish this condition with pharmacological trophic factors that affect neurogenesis and plasticity.

\*DoD-276, “Identification of Lipid Biomarkers of Inflammation and Metabolic Disturbances in GWI” will examine the possible usefulness of omega-6 and omega-3 fatty acid, mitochondria specific lipids (cardiolipin and acylcarnitines), and peroxisome function specific very long chain fatty acids (VLCFA) and branched chain fatty acids (BCFA) as biomarkers of GWI. Lipids will be examined in blood samples from three mouse models of GWI using liquid chromatography/mass spectrometry (LC/MS). Lipids that indicate differential response to GW exposure and are altered at several chronic post-exposure time points across the mouse models will be examined in blood samples collected from Veterans with GWI and controls from the GW era.

\*DoD-277, “Treatment of Memory Disorders in Gulf War Illness with High-Definition Transcranial Direct Cortical Stimulation” is designed to determine if 1-milliamp anodal HD tDCS is an effective treatment for verbal retrieval deficits in GWI. This study will attempt to entrain the verbal retrieval circuit using HD tDCS to target the pre-supplementary motor area in order to improve retrieval in impaired GWI patients, using behavioral and electrophysiological markers to assess outcomes.

\*DoD-278, “Metabolomics Distinguish Veterans with Gulf War Illness: Replicating and Expanding Promising Results” will follow up a prior study that identified a spectrum of critical, previously unidentified objective changes in Gulf War Veterans with Gulf War illness (GWI). Previously identified changes match pathways reported to be altered in reports of metabolomic and lipid alterations in mitochondrial dysfunction. Use of this approach completely separated GWV with GWI from controls matched in age, sex, and ethnicity. This study will expand key insights into pathways and mechanisms in GWI and may provide an objective means to diagnose GWI.

\*DoD-279, “Neurodegenerative Changes after Exposure to Gulf War Insults” will use an established mouse model of Gulf War exposures to identify induced changes in the CNS connectivity/neuroprotective pathway followed by administration of a dietary treatment to upregulate activity of the Nrf2 transcription factor to improve neuronal health.

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\*DoD-280, “Curcumin Nanoparticle Therapy for Gulf War Illness” will test oral administration of an optimal dose of curcumin encapsulated in biodegradable polymer nanosystems (nCUR) and its ability to alleviate cognitive, memory, and mood impairments associated with GWI via suppression of oxidative stress and inflammation and increased neurogenesis in the hippocampus.

\*DoD-281, “Exploring Mechanisms Underlying Impaired Brain Function in Gulf War Illness through Advanced Network Analysis” is designed to map the whole-brain resting state network architecture of GWI Veterans and compare them with age-matched Veteran controls.

\*DoD-282, “Gulf War Women's Health Cohort” will focus on (1) establishing a large sample of women Veterans who served in the 1990-1991 Gulf War, and a comparison group of women who served in other locations during that period, (2) providing current, comprehensive data on the health status of these women, and (3) identifying any specific conditions that affect GW women Veterans at excess rates.

\*DoD-283, “Therapeutic Inhibition of microRNA-124 for the Treatment of Gulf War Illness” will investigate the therapeutic efficacy of a locked nucleic acid (LNA)-antisense oligonucleotide (LNA-antimiR-124) to improve learning and memory impairments, depressive-like behavior, and neuroendocrine dysfunction in an established rat model of GWI.

\*DoD-284, “Alleviating Headache and Pain in GWI with Neuronavigation-Guided rTMS” is a clinical trial that will compare the effect of active repetitive transcranial magnetic stimulation (rTMS) at the left motor cortex with sham rTMS to reduce symptoms of GWI-related headaches and pain (GWI-HAP). The study will compare the treatment effect in improving joint and muscle pain, attentional cognitive function, fatigue, depression, and sleep disturbance as secondary outcome measures.

\*DoD-285, “Disentangling the Effects of PTSD from GWI for Improved Diagnostics and Treatments” is designed to perform a secondary systems biology analysis based on resources, methodology, and results from ongoing GWI research initiative to (1) isolate bio-behavioral profiles that are specific to GWI alone, (2) evaluate how immune regulation in GWI is modified in the presence of probable PTSD diagnosis, and (3) use ongoing work in predictive modeling to assess possible changes to treatment of GWI in the context of probable PTSD diagnosis.

\*DoD-286, “Persistently Elevated Somatic Mutation as a Biomarker for Clinically Relevant Exposures in GWI” will compare military Veterans deployed to the Gulf to those who were not deployed using a glycoprotein A (GPA) mutation assay to identify an association of somatic mutation frequency with both common and rare components of GWI, such as chronic fatigue syndrome and cancer.

\*DoD-287, “Improving Cognitive Function in Veterans with Gulf War Illness by Improving Cerebral Vascular Function” is designed to link the reduced ability of cerebrovascular

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dilation to cognitive impairments seen in GWI. Researchers will determine if Veterans with GWI that have cognitive impairment also demonstrate an impaired ability to dilate their cerebral vessels. This study will also determine if low cerebrovascular reactivity can be restored by blocking COX and as a result, improve cognitive function.

\*DoD-288, "Pyridostigmine Bromide, the Enteric Nervous System, and Functional Gastrointestinal Disorders in Gulf War Illness" will attempt to understand how the anti-nerve gas drug PB contributes to the development of functional GI disorders in Gulf War illness. Investigators propose that controlling reactive gliosis in the enteric nervous system with the anti-inflammatory drug palmitoylethanolamide (PEA) is a novel therapeutic approach that will improve gut dysfunction induced by PB.

\*DoD-289, "Investigating Increased Glutamate Transporter EAAT2 Function as a Potential Therapeutic Approach for Gulf War Illness" will study the hypothesis that chronic exposure to GWI-related chemicals and stress results in an increase in extracellular glutamate levels and the dysfunction of the glutamatergic system leading to hippocampal damages and subsequent cognitive and mood deficits. Enhanced glutamate uptake function by increased expression of the glutamate transporter EAAT2 is proposed to normalize the dyshomeostasis of the glutamatergic system and subsequently restore normal synaptic and astrocytic function. This, in turn, may result in improvement of cognitive functions and amelioration of depression and anxiety symptoms.

\*DoD-290, "Mitochondrial Dysfunction and Gulf War Illness" will investigate the hypothesis that mitochondrial dysfunction is an important contributor to GWI. An important corollary hypothesis is that mitochondrial parameters measured in peripheral blood mononuclear cells (PBMCs) are a biomarker for mitochondrial dysfunction in affected tissues. In a small preliminary cohort, these investigators have obtained strong data supporting the hypothesis that mitochondrial health is impaired in PBMCs of Veterans with GWI. To test the hypothesis, mitochondrial parameters in PBMCs of a larger cohort of GWI cases and controls will be measured. The stability of mitochondrial parameters over time as well as the role of multiple factors as drivers of mitochondrial function will be investigated.

\*DoD-291, "Identification of Causes and Treatments for Chronic Pain in a Model of Gulf War Illness" will investigate whether musculoskeletal pain, which is mediated by neuroinflammatory signaling in a GWI rat model, can be successfully treated by clinically relevant, systemically administered drugs targeting key sites along the neuroinflammatory pathway. The success of these drugs in advanced preclinical development and/or with Food and Drug Administration (FDA) approval will expedite their translation to successful clinical application.

\*DoD-292, "Therapeutic Intervention of Glial-Mediated Enhancement of Neuroinflammation in an Established Model of GWI" will characterize the contribution of different durations of high physiological stress and glial cell types on the phenotype of an established corticosterone (CORT)-primed diisopropyl fluorophosphate (DFP) model of Gulf War illness (GWI) and test the therapeutic potential of Food and Drug Administration (FDA)-approved inflammatory and cell-type specific inhibitors anakinra and etanercept.

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\*DoD-293, "Evaluation of Treatment Efficacy with a Potent Novel Immunomodulatory Glycan Conjugate in Gulf War Illness Models" will test a novel immunotherapeutic, a glycan conjugate, which is a component of human milk, in two different mouse models of GWI. One of the models consists of a 10-day pyridostigmine bromide/permethrin (PB/PM) treatment; the other model utilizes PB, the insect repellent DEET, the sarin surrogate DFP, and stress (PB/DEET/DFP/stress), with the exposure paradigm spanning 15 days. Investigators propose that in both GWI models, glycan (LNFP III) conjugate treatment, even when initiated months after exposure to the GWI chemicals has ended, will restore immune system balance in the periphery and in the brain.

\*DoD-294, "Improving Diagnostics and Treatments for GWI Females by Accounting for the Effects of PTSD" will build on ongoing research directed at mapping complex inflammatory mechanisms in GWI to improve understanding of the immunologic underpinnings of GWI in women and the compounding effects of comorbidity with PTSD. The current proposal focusing on women is intended to serve as a complementary study to a similar ongoing analysis in men.

\*DoD-295, "GWI: Molecular Analysis of Disease Endophenotypes and Response to Acupuncture Treatment" will undertake a comprehensive plasma proteomics analysis using a recently developed and highly sophisticated screening technology (SOMAscan) that multiplexes 1,310 proteins. By applying bioinformatics and machine learning tools in combination with systems biology approaches, investigators will generate signatures, classifiers, and disease interactive networks that define GWI. A thorough validation process will follow the identification of differentially expressed proteins. The goal is not only to devise a highly sought diagnostic test for GWI, but also to gain, via the study of the GWI proteome, insights about disease mechanisms that will pave the way to develop targeted therapies. In parallel, the PI will take advantage of the fact that in the parent GWI cohort patients were treated with acupuncture and will search for the elusive "acupuncture biological signature". Finally, intra-patient variability in symptom experience, psychosocial variables and response to acupuncture will be captured with specific sets of serum proteins.

\*DoD-296, "Susceptibility of Cathepsin A to Organophosphate Pesticides and Nerve Agents" will investigate the hypothesis that fibromyalgia syndrome (FMS)-like symptoms of GWS may arise from organophosphate (OP)-inhibition of the serinyl cathepsin, CatA. Investigators will characterize the organophosphate inhibitor susceptibilities of CatA, using a set of OP pesticides and simulants. They will confirm nerve agent inhibition by demonstrating effects of OP-inhibition on the activity and stability of NEU1/CatA and beta-galactosidase(bGal)/CatA complexes.

\*DoD-297, "Quantitative Acute and Chronic Assessments of Gulf War Chemical Toxicity in Rats Using Neuroelectrophysiological Measurements and PBPK Models" will characterize CNS function using multiple electrophysiological (EP) approaches and calculate the time course and concentrations of Gulf War chemicals DEET, pyridostigmine bromide (PB), and permethrin in the brain using physiologically based pharmacokinetic (PBPK) models.

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Investigators will develop an in vitro model of GWI using brain slices exposed to Gulf War chemicals, at concentrations similar to those predicted by the PBPK model. An assessment of the effectiveness of potential countermeasures (e.g., luteolin) to mitigate the neuronal dysfunction induced by Gulf War chemicals will be performed.

\*DoD-298, “Computer-Aided Decoding of Brain-Immune Interactions in Gulf War Illness (GWI): A Joint Embedding on Brain Connectomic and Immunogenomic Markers” will employ a novel classification framework based on a combination of brain connectomics and immuno-genetic (genomic) approaches of GWI to develop novel computer-based diagnostic systems and features.

\*DoD-299, “Sigma-1 Receptor Agonists as a Novel Therapeutic for Brain Mitochondrial Dysfunction in Gulf War Syndrome” will investigate the therapeutic efficacy of selected S1R agonists in relieving cognitive degradation in an established GWI mouse model. Investigators hypothesize that S1R agonists improve cognitive abilities through effectively restoring mitochondrial energy metabolism in neurons and enhancing neuroplasticity in GWI mice.

\*DoD-300, “A Pilot RCT on the Effect of Resveratrol on Mood, Memory Deficits, Hippocampal Inflammation, and Neurogenesis in Veterans with Gulf War Illness (GWI)” will evaluate the effect of the over-the-counter antioxidant supplement resveratrol (RESV), a polyphenol found abundantly in the skin of red grapes and that is known to have robust antioxidant and anti-inflammatory properties, on cognitive function, memory, functional status, and mood in Veterans who suffer from GWI. Investigators will also evaluate the effects of RESV on neurogenesis, functional connectivity, and functional status in the hippocampus and examine any anti-inflammatory and antioxidant effects.

\*DoD-301, “Growth Hormone-Releasing Hormone (GHRH) Antagonist: Evaluation of Beneficial Effects for Gulf War Illness” will use an existing model of GWI to evaluate new therapeutic alternatives to alleviate GWI based on the beneficial effects of highly biologically active analogs (antagonists) of GHRH.

\*DoD-302, “Investigating Gene-Environment Interactions in Multiple Cohorts of 1990-1991 Gulf War Veterans” will determine the contribution of BChE genotype to the development of GWI overall, in relation to PB and other cholinergic exposures in theater, and in combination with effects of PON1-192 genetic status.

\*DoD-303, “Direct Current Stimulation for Pain Treatment of Gulf War Illness” will conduct a prospective, double-blind, placebo controlled, randomized, parallel-group study to evaluate the efficacy and safety of a novel therapy to treat pain complaints for Veterans diagnosed with Gulf War illness. A new treatment option using tDCS has been developed by this group for the management of fibromyalgia complaints. This approach is being directly translated to Gulf War Veterans with pain symptoms since they report a similar disability, meet the criteria for fibromyalgia, and seem to have a similar neural mechanism underlying the pathology.

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\*DoD-304, “Human Leukocyte Antigen in Gulf War Veterans: Association with Symptoms and Inflammatory Markers” will evaluate the association of genotype, GWI symptomatology, and biomarkers of immune system dysfunction, inflammation, and autoimmunity in a large sample of Gulf War era Veterans to better understand the pathogenesis and pathophysiology of GWI and ultimately inform treatment decisions for affected Veterans.

\*DoD-305, “Glutamate Receptor and Kynurenine Pathway Functioning in the Pathobiology of Gulf War Illness” will characterize CNS kynurenine pathways (KP) and glutamatergic N-methyl-D-aspartate receptor (NMDAR) functioning in a well-characterized sample of 1991 Gulf War Veterans. Associations with other markers of central inflammation, and with GWI symptom severity, will be investigated. Investigators hypothesize higher quinolinic acid or protective kynurenic acid (KYNA) kynurenines produced by KP and more pronounced NMDAR activity will be seen in GWI cases than in Gulf War Veteran controls.

\*DoD-306, “Mitochondrial Dysfunction and Aberrant Immune Activation in the Pathobiology of Gulf War Illness” will investigate the etiology of GWI in terms of mitochondrial dysfunction and subsequent immune activation. Investigators hypothesize that persistent mitochondrial dysfunction is an important driver of GWI pathobiology, and propose that mitochondrial dysfunction aberrantly engages the innate immune system to enhance inflammatory and interferon responses, thus exacerbating GWI symptoms. This study will test whether bezafibrate, a Food and Drug Administration-approved, lipid-lowering drug that boosts healthy mitochondrial function and lowers inflammation, will alleviate neuropathology and cognitive dysfunction in a rodent model of GWI.

\*DoD-307, “Identification of Causes and Treatment for Chronic Depression in a Rodent Model of Gulf War Illness” is designed to probe the molecular basis of GWI depression by addressing the hypothesis that chronic DFP exposure upregulates NMDA-Rs (N-methyl-D-aspartate receptors), which activate Ca<sup>2+</sup> induced Ca<sup>2+</sup> release mechanisms leading to sustained neuronal Ca<sup>2+</sup> elevations, and treatment with KET will revert these elevated Ca<sup>2+</sup> levels to baseline, thereby exerting a rapid and long-lasting antidepressant effect with minimal toxicity in GWI rodents.

\*DoD-308, “Genetic Basis of Individual Differences in Susceptibility to Gulf War Illness” will measure genetic variation in neuroinflammatory gene expression response to corticosterone, DFP, and their combination in 40 BXD recombinant mouse strains. Investigators will conduct genetic mapping to identify candidate genes underlying differential transcriptional response to DFP and corticosterone + DFP. Investigations will include gene network and gene ontology analysis.

\*DoD-309, “Gene Expression to Advance Understanding, Aid Diagnosis, and Define Treatment Targets in Gulf War Illness” will use recombinant mice strains to test whether genes play a role in determining who develops GWI. Investigators will treat mice with a combination of DFP and CORT, will measure symptoms and brain changes, and correlate genes that are involved in these differences.

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\*DoD-310, “Melatonin for Reversing Brain Dysfunction in Gulf War Illness” is designed to test whether increased oxidative stress, chronic inflammation, and declined neurogenesis in the hippocampus along with systemic inflammation are among the major causes underlying cognitive, memory, and mood impairments in GWI. Investigators propose to test the efficacy of oral administration of melatonin (MEL; a hormone synthesized mainly by the pineal gland and having robust antioxidant and sleep-inducing properties) for easing cognitive, memory, and mood dysfunction in a rat model of GWI.

\*DoD-311, “The Role of Oxidative Stress and Mitochondrial Dysfunction in Cognitive Impairments in Gulf War Illness” will use an established mouse GWI model to investigate the pathogenic mechanism of GWI, with the ultimate goal of identifying effective therapeutic approaches to improve the neurocognitive functions in GWI Veterans. This project proposes two specific aims. Aim 1 will determine how Gulf War agents affect mitochondrial functionality in the CNS over time following exposure and identify the root causes that perpetuate mitochondrial dysfunction. Aim 2 will evaluate therapeutic strategies, focusing on improving mitochondrial functions, using genetic and pharmacological approaches, and evaluate their efficacies against cognitive impairments in GWI.

\*DoD-312, “Identification of Epigenetic Signatures as Biomarkers of Gulf War Illness” will use integrated approaches to investigate epigenetic changes of GWI and correlate the epigenetic changes with GW-relevant exposures (including pyridostigmine bromide [PB], pesticides, sarin) to identify the biological indicators in GWI pathogenesis in a well-established cohort of Gulf War Veterans from the large multi-site Department of Defense-funded Boston Gulf War Illness Consortium (GWIC) (GW120037). Identified epigenetic changes associated with GWI may lead to additional treatment options for Veterans with GWI by targeting these changes.

\*DoD-313, “Measurement of Biomarkers in Samples Collected in a Coenzyme Q10 Treatment Trial in Gulf War Illness and Control Subjects” will expand on the promising Phase I/II results tied to Coenzyme Q10 (CoQ10). A Department of Veterans Affairs (VA) clinical trials group headed by Dr. Nancy Klimas was awarded funding to initiate a Phase III placebo control treatment trial of CoQ10. However, this clinical trial does not include studies of biomarkers in the context of baseline and treatment response but does include collection, shipping to the Miami VA, processing and cryopreservation of plasma and peripheral blood mononuclear cells (PBMC) at baseline and during the trial. The current project will examine biomarkers useful as surrogates of severity as well as predictors of response to CoQ10 therapy.

\*DoD-314, Partnered award to DoD-313, “Measurement of Biomarkers in Samples Collected in a Coenzyme Q10 Treatment Trial in Gulf War Illness and Control Subjects” will expand on the promising Phase I/II results tied to Coenzyme Q10 (CoQ10). A Department of Veterans Affairs (VA) clinical trials group headed by Dr. Nancy Klimas was awarded funding to initiate a Phase III placebo control treatment trial of CoQ10. However, this clinical trial does not include studies of biomarkers in the context of baseline and treatment response but does include collection, shipping to the Miami VA, processing and



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cryopreservation of plasma and peripheral blood mononuclear cells (PBMC) at baseline and during the trial. The current project will examine biomarkers useful as surrogates of severity as well as predictors of response to CoQ10 therapy.

\*DoD-315, “Persistent Hormonal Changes in Veterans with Gulf War Illness” will assess the association of GWI with dysregulation of the major pituitary hormonal systems: the growth hormone (GH) axis, gonadotropin axes, thyroid hormone axis, and HPA axis. Hormone measures (including the frequency of hormone deficiencies) between Gulf War Veterans with and without GWI will be compared. The study will also evaluate the relationship between endocrine measures and neurocognitive function through a series of neuropsychological assessments in Veteran subgroups defined by (a) the presence/absence of comorbid psychiatric conditions (e.g., post-traumatic stress disorder, depression), (b) individual and combined characteristics of deployment (e.g., participation in combat, exposures in theater), and (c) degree of symptomatology in GWI symptom domains.

\*DoD-316, “Treatment Strategies in a Mouse Model of Chronic Gulf War Illness” will validate targeting neuroinflammation as a therapeutic by extending pilot studies testing the long term (7-month) effects of treatment with the anti-inflammatory Anatabine in a mouse model of GWI. Investigators will determine whether or not a combined therapeutic approach with Anatabine will mitigate the effects of Gulf War agent exposure more effectively than a single compound approach.

\*DoD-317, “Genomic Approach to Find Female-Specific Mechanisms of GWI Pathobiology” will combine the latest state-of-the-art genomics and computational biology methods to identify novel, female-specific mechanisms of transcriptional regulation in GWI, which will facilitate better understanding of GWI pathobiology in women and provide further insights in mechanisms of GWI in men.

\*DoD-318, “Glutamate Neuroexcitotoxicity in GWI” will test the effectiveness of a low-glutamate diet in GWI patients, as a way to mediate symptom occurrence by reducing excess glutamatergic neurotransmission.

\*DoD-319, “The Use of B-Cell Depletion Therapy (BCDT) in Gulf War Illness: A Phase 1/2 Study” aims to target two different immune pathways, the pro-inflammatory cytokine cascade as well as interfering with autoantibody production. By inhibiting autoantibody production using a B-cell depleting therapy, investigators not only hope to decrease the presence of autoantibodies but decrease pro-inflammatory cytokine expression and reset underlying mechanisms of disease by wiping out B-cell memory cells to prevent future autoantibody production.

\*DoD-320, “Role of Vestibular Hypofunction in Exacerbating Autonomic Dysfunction in Gulf War Illness” will examine the role of vestibular dysfunction and its effect on autonomic function. One hundred Veterans with GWI and 50 Gulf War Era Veterans will be screened. Investigators will determine if Veterans with GWI that have impaired vestibular function also demonstrate impaired autonomic function.

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\*DoD-321, “Gender and Gulf War Illness” will use a GWI female mouse model to study cardiovascular and neuro-inflammatory profiles in response to DFP exposure to test whether responses correlate with interactions between the gender-specific sex steroids. The study will include examination of responses to drug therapies including Enbrel (ENB), Mifepristone (MIF), or the combination (ENB+MIF) (modulator of TNF- $\alpha$  and adrenocorticoid receptor, respectively).

\*DoD-322, “Tau Pathology as a Contributor to Gulf War Illness and a Basis for Potential Therapy” will differentiate various subtypes of human central nervous system neurons derived from a Gulf War repository bank of human induced pluripotent cells (hiPSCs) and examine tau pathology with and without GWI toxicant exposures. Investigators will also screen for potential therapeutic inhibitory compounds and antibodies to alleviate tau phenotypes as well as microtubule stability defects.

\*DoD-323, “Identifying Novel Immune and Radiographic CT Imaging Signatures of Chronic Bronchiolitis” will investigate the abnormal pulmonary immune function associated with airway injuries that promote the development of chronic bronchiolitis (CB), a disorder characterized by symptoms of cough, dyspnea, and fatigue resulting from persistent airway inflammation and fibrosis lasting years after exposure. CT scans from Gulf War Veterans with pulmonary symptoms will be used in this study.

\*DoD-324, “Next-Generation Biomarkers of Gulf War Illness” will utilize state-of-the-art proteomic and epigenetic technologies to identify unique molecular markers in the blood of ill Gulf War Veterans.

### **VA Funded Projects**

VA initiated funding for eight new projects during FY 2016. These eight projects focused on Brain and Nervous System Function (1) and Symptoms and General Health (7).

VA-198, “Healthcare utilization patterns and associated costs for Gulf War I Era Veterans” is designed to describe the demographics and characteristics of a cohort of Veterans of the 1990-1991 era; to describe healthcare utilization patterns and direct care costs both overall, deployed versus non-deployed Veterans, and for Gulf War illness, cardiovascular conditions, mental health disorders, and complex chronic disease; and to explore patients' decision-making perspectives regarding choice of healthcare location and utilization.

VA-199, “Post-Exertion Malaise in GWI: Brain Autonomic and Behavioral Interactions” will study the mechanisms of symptom maintenance and exacerbation in Veterans suffering with Gulf War illness (GWI). Multiple physiological systems (CNS, autonomic, immune) will be monitored in Veterans with and without GWI. The impact of an exercise challenge (post-exertional malaise) on CNS regulation of pain/fatigue, cardiovascular autonomic function, and immune system activity will be evaluated to determine whether interactions

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among multiple systems significantly explain symptoms of GWI. This study could lead to treatments for GWI that are mechanistically based on physiology.

VA-200, “A Translational Medicine Approach to Gulf War Illness: From Cells to Therapy” will attempt to conduct a systematic assessment and characterization of the therapeutic effects of drugs that impact five physiological targets which were selected on the basis of experimental evidence analyzed in a systems biology model. The drug/target pairs can be tested and validated by observing the effects of the therapeutic agents on *in vitro* cultures of peripheral blood mononuclear cells (PBMCs) from GWI patients and controls. The study will advance the understanding of the underlying mechanisms of GWI using targeted therapies *in vitro* before human clinical trials are conducted.

VA-201, “WRIISC as a Model of Care for Chronic Multisymptom Illness” will look into the reasons why 97% of Veterans with GWI who are referred to VA’s War Related Illness and Injury Study Center are satisfied with the health care they receive. One hundred patients from the WRIISC and 100 patients from other VA medical centers will be followed for 12 months to determine if their degree of satisfaction correlates with their adherence to treatment plans. The most effective components of the WRIISC model of health care would then be integrated into other VA medical centers.

VA-202, “Gulf War Neurotoxicants and Acquired Cognitive and Neuropsychological Dysfunction” will use male and female rats to evaluate the effect of lipopolysaccharide (LPS), alone and with oral pyridostigmine (PB), on the severity and persistence of neuroinflammation and resulting neurofunctional abnormalities. Inflammatory cytokines in CSF and plasma will be measured, tissue neuroinflammation will be examined, and microstructural and metabolic changes will be studied after exposure to LPS and PB. After symptom onset, the effect of treatment with a PPAR $\gamma$  agonist on neuroinflammation will be evaluated.

VA-203, “Novel Interventions for Gulf War Veterans’ Illnesses” will compare the effectiveness of Tai Chi with a Stretching and Wellness Education Intervention in two groups of 60 patients each who meet criteria for GWI with significant chronic pain. After a 12-week treatment period, there will be nine months of follow-up to monitor the long-term effects of these non-pharmacologic treatments for pain. Secondary outcome measures that are expected to improve include fatigue, cognition, quality of life, and physical functioning.

VA-204, “Pilot Test of Telephone-Delivered Cognitive Behavioral Therapy for Insomnia for Veterans with Gulf War Illness” is a two-arm, randomized controlled trial to investigate the efficacy of CBT-I for sleep and non-sleep GWI symptoms in 64 Veterans with GWI. Half of the Veterans will be randomized to CBT-I and half to a treatment-as-usual control group. The primary outcomes will be effect sizes of pre- to-post-treatment changes and maintenance of treatment effects at 6 months in the group randomized to CBT-I. This non-

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pharmacologic intervention is also expected to treat some of the non-sleep symptoms associated with GWI.

VA-205, "A Randomized, Double-blind Placebo-controlled Phase III Trial of Coenzyme Q10 in Gulf War Illness" will assess the clinical efficacy and safety of CoQ10 (ubiquinol) in 200 Veterans with GWI, in a double-blind, randomized, placebo-controlled trial, with 100 participants per treatment arm of the study. Subjects will be recruited at four geographically different sites over the course of the 6-month intervention. The primary objective is to assess efficacy, and secondary endpoints will include objective measures of activity and cognitive function as well as an evaluation of putative biomarkers for their ability to predict severity and response to therapy.

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# **Appendices**

## **Federally Funded Research Projects**

# **Appendix A**

## **Project Index By Department**

## DEPARTMENT OF DEFENSE PROJECTS

- DoD-001 Naval Health Study Program
- DoD-001A Epidemiologic Studies of Morbidity Among GW Veterans: A Search for Etiologic Agents and Risk Factors; A Study of Symptoms Among 1500 Seabees
- DoD-001B Epidemiologic Studies of Morbidity Among GW Veterans: A Search for Etiologic Agents and Risk Factors; Study 2: A Comparative Study of Hospitalizations among Active-Duty Personnel Who Participated in the Gulf War and Similar Personnel Who Did Not
- DoD-001C Epidemiologic Studies of Morbidity Among GW Veterans: A Search for Etiologic Agents and Risk Factors; Study 3: A comparative study of pregnancy outcomes among GW Veterans and other active-duty personnel
- DoD-001D Epidemiologic Studies of Morbidity Among GW Veterans: A Search for Etiologic Agents and Risk Factors; Study 4: Infertility and Miscarriage in GW Veterans
- DoD-001E Epidemiologic Studies of Morbidity Among GW Veterans: A Search for Etiologic Agents and Risk Factors; Study 5: Seabee Health Study
- DoD-001F Epidemiologic Studies of Morbidity Among GW Veterans: A Search for Etiologic Agents and Risk Factors; Study 6: A Comparison of Nonfederal Hospitalization Experience Among Veterans in California who have separated from active service: GWV vs. NDV
- DoD-001G Epidemiologic Studies of Morbidity Among GW Veterans: A Search for Etiologic Agents and Risk Factors; Study 7: Prevalence of Congenital Anomalies Among Children of Persian GW Veterans
- DoD-002 Physiological and Neurobehavioral Effects in Rodents from Exposure to Pyridostigmine, Fuels, and DEET
- DoD-004 The General Well-Being of Gulf War Era Service Personnel from the States of Pennsylvania and Hawaii: A Survey
- DoD-007A Health Risk Assessment of Embedded Depleted Uranium: Behavior, Physiology, Histology, and Biokinetic Modeling
- DoD-007B Carcinogenicity of Depleted Uranium Fragments
- DoD-008A Serologic Diagnosis of Viscerotropic Leishmaniasis (VTL)
- DoD-008B Development of a Leishmania Skin Test Antigen (LSTA)
- DoD-009 Identification of the Genetic Factors Which Control Tropism in Leishmania
- DoD-010 Pyridostigmine Synergistic Toxicity Study
- DoD-011 Male/Female Differential Tolerances to Pyridostigmine Bromide
- DoD-013 Effects of Persian Gulf War Service on Military Working Dogs
- DoD-014 Risk Factors Among US Army Soldiers for Enrolling on the Department of Veterans Affairs Gulf War Registry
- DoD-015 Comparative Mortality Among US Military Personnel Worldwide During Operations Desert Shield and Desert Storm

DoD-016 Kuwait Oil Fire Health Risk Assessment

DoD-017 Retrospective Studies Involving Military Use of Pyridostigmine as a Pretreatment for Nerve Agent Poisoning

DoD-018 Kuwait Oil Fires Troop Exposure Assessment Model (TEAM)

DoD-019 Persian Gulf Veterans Health Tracking System

DoD-021 Study of Variability in Pyridostigmine Inhibition of Blood Cholinesterases in Healthy Adults and Individuals with Symptoms Following Participation in Operation Desert Storm

DoD-022 Chronic Organophosphorus Exposure and Cognition

DoD-023 Acute and Long-Term Impact of Deployment to Southwest Asia on the Physical and Mental Health of Soldiers and their Families

DoD-030 Epidemiological Studies Persian Gulf War Illnesses, PG Women's Health Linkage Study

DoD-031 Dysregulation of the Stress Response in the Persian Gulf Syndrome

DoD-032 Neuropsychological Functioning in Persian Gulf Era Veterans

DoD-033 Effects of Pyridostigmine in Flinders Line Rats Differing in Cholinergic Sensitivity

DoD-034 Characterization of Emissions from Heaters Burning Leaded Diesel Fuel in Unvented Tents

DoD-035 Feasibility of Investigating Whether There is a Relationship Between Birth Defects and Service in the Gulf War

DoD-036 Fatigue in Persian Gulf Syndrome-Physiologic Mechanisms

DoD-037 Neurobehavioral and Immunological Toxicity of Pyridostigmine, Permethrin, and DEET in Male and Female Rats

DoD-038 Diagnostic Antigens of *Leishmania tropica*

DoD-039 A Controlled Epidemiological and Clinical Study into the Effect of Gulf War Service on Servicemen and Women of the United Kingdom Armed Forces

DoD-040 Psychological and Neurobiological Consequences of the Gulf War Experience

DoD-041 Evaluation of Muscle Function in Persian Gulf Veterans

DoD-042 The Symptomatic Persian Gulf Veterans Protocol: An Analysis of Risk Factors with an Immunologic and Neuropsychiatric Assessment

DoD-044 Investigation of Seminal Plasma Hypersensitivity Reactions

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- DoD-085 CNS Cytokines and CRH in GW Veterans with Multiple Unexplained Symptoms
- DoD-086 Effects of Combat Stress on Structure and Function of the Hippocampus
- DoD-087 Measurement and Validation of Psychosocial Risk and Resilience Factors Accounting for Physical and Mental Health and Health-Related Quality of Life among PGWVs
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- DoD-089 Limbic Blood Flow and Opiate Receptor PET in Posttraumatic Stress Disorder
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- DoD-113 Interactions of Subsymptomatic Doses of Sarin with Pyridostigmine: Neurochemical, Behavioral, and Physiological Effects
- DoD-114 A Re-examination of Neuropsychological Functioning in Persian GW Veterans
- DoD-115 A Randomized, Multi-Center, Controlled Trial of Multi-Model Therapy in Veterans with Gulf War Illnesses (EBT) (See also VA-62; formerly VA/DoD 1D)
- DoD-116 VA/DoD Core Funding of the Medical Follow-Up Agency (See also VA-63; formerly VA-DoD-2D/2V)
- DoD-116A Follow-Up Investigation of Troops Exposed to Nerve Agents at Aberdeen Proving Ground (Pilot Study) (See also VA-63A; formerly VA/DoD-2DA)
- DoD-116B Patterns of Pre-Persian Gulf War Illness and Health Care Seeking, Pilot Study (See also VA-63B; formerly VA/DoD- 2DB)
- DoD-117 Patterns of Pre-Persian Gulf War Illness and Health Care Seeking
- DoD-118 An Epidemiological Investigation into the Occurrence of Amyotrophic Lateral Sclerosis (ALS) Among GW Veterans (See also VA-61)

- DoD-119 Antibiotic Treatment of GW Veterans' Illnesses (ABT) (See also VA-55)
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- DoD-131 Magnetic Resonance and Spectroscopy of the Human Brain in Gulf War Illnesses
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- DoD-140 US DOD Surveillance for Neoplasms in Infancy
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- DoD-142 Illnesses Among Persian GW Veterans: Case Validation Studies (Iowa / Great Britain)

- DoD-143 Millennium Cohort Study (See also VA-78)
- DoD-144 Psychological Health Screening: Methods and Metrics for Deployed Forces
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- DoD-147 Development and Validation of the Automated Neuropsychological Assessment Metric (ANAM) for Deployment Health Monitoring Applications
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- DoD-165 Biomarkers for Amyotrophic Lateral Sclerosis in Active Duty Military – BALSAM
- DoD-166 A Placebo-Controlled Trial of Prazosin vs. Paroxetine in Combat Stress-Induced PTSD Nightmares and Sleep Disturbance

- DoD-167 Mass Spectrometry to Identify New Biomarkers of Nerve Agent Exposure
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- DoD-247 Neurovascular and Autonomic Dysfunction Associated with Gulf War Illness Pain
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- DoD-249 Effect of Diet on Gulf War Illness: A Pilot Study
- DoD-250 An Integrated Genomics and Cell Biology Approach to Correlate Novel GWI Indicators of Infections and Neuroinflammatory Mechanisms with Targeted Drug
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- DoD-252 Preclinical Treatment of an Organophosphate Model of Gulf War Illness
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- DoD-287 Improving Cognitive Function in Veterans with Gulf War Illness by Improving Cerebral Vascular Function



- DoD-288 Pyridostigmine Bromide, the Enteric Nervous System, and Functional Gastrointestinal Disorders in Gulf War Illness
- DoD-289 Investigating Increased Glutamate Transporter EAAT2 Function as a Potential Therapeutic Approach for Gulf War Illness
- DoD-290 Mitochondrial Dysfunction and Gulf War Illness
- DoD-291 Identification of Causes and Treatments for Chronic Pain in a Model of Gulf War Illness
- DoD-292 Therapeutic Intervention of Glial-Mediated Enhancement of Neuroinflammation in an Established Model of GWI
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- DoD-294 Improving Diagnostics and Treatments for GWI Females by Accounting for the Effects of PTSD
- DoD-295 GWI: Molecular Analysis of Disease Endophenotypes and Response to Acupuncture Treatment
- DoD-296 Susceptibility of Cathepsin A to Organophosphate Pesticides and Nerve Agents
- DoD-297 Quantitative Acute and Chronic Assessments of Gulf War Chemical Toxicity in Rats Using Neuroelectrophysiological Measurements and PBPK Models
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- DoD-300 A Pilot RCT on the Effect of Resveratrol on Mood, Memory Deficits, Hippocampal Inflammation, and Neurogenesis in Veterans with Gulf War Illness (GWI)
- DoD-301 Growth Hormone-Releasing Hormone (GHRH) Antagonist: Evaluation of Beneficial Effects for Gulf War Illness
- DoD-302 Investigating Gene-Environment Interactions in Multiple Cohorts of 1990-1991 Gulf War Veterans
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- DoD-307 Identification of Causes and Treatment for Chronic Depression in a Rodent Model of Gulf War Illness
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- DoD-311 The Role of Oxidative Stress and Mitochondrial Dysfunction in Cognitive Impairments in Gulf War Illness
- DoD-312 Identification of Epigenetic Signatures as Biomarkers of Gulf War Illness
- DoD-313 Measurement of Biomarkers in Samples Collected in a Coenzyme Q10 Treatment Trial in Gulf War Illness and Control Subjects
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- DoD-317 Genomic Approach to Find Female-Specific Mechanisms of GWI Pathobiology
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- HHS-001 Health Assessment of Persian GW Veterans from Iowa
- HHS-002 Disease Cluster in a Pennsylvania Air National Guard Unit, EPI-AID 95-18
- HHS-003 Biomarkers of Susceptibility and Polycyclic Aromatic Hydrocarbon (PAH) Exposure in Urine and Blood Cell DNA from U.S. Army Soldiers Exposed to Kuwaiti Oil Well Fires
- HHS-004 Suspected Increase of Birth Defects and Health Problems Among Children Born to Persian GW Veterans in Mississippi
- HHS-005 Cognitive Function and Symptom Patterns in Persian Gulf Veterans
- HHS-006 Defining Gulf War Illness
- HHS-007 Immunotoxicity of Dermal Permethrin and Cis-Urocanic Acid
- HHS-008 Strategy to Identify Non-Additive Response to Chemical Mixtures
- HHS-009 Improving Health Risk Communications to Prevent Unexplained Illnesses Related to Military Deployments
- HHS-010 Health-e Voice: Optimized Implementation of a Stepped Clinical Risk Communications Guideline
- HHS-011 Deployment to the Gulf War and the Subsequent Development of Cancer
- HHS-012 Genetic Epidemiology of ALS in Veterans

## **DEPARTMENT OF VETERANS AFFAIRS PROJECTS**

VA-001	Mortality Follow-up Study of Persian Gulf Veterans
VA-002	National Health Survey of Persian Gulf Veterans
VA-002A	VA National Survey of Persian Gulf Veterans - Phase I
VA-002B	VA National Survey of Persian Gulf Veterans - Phase II
VA-002C	VA National Survey of Persian Gulf Veterans - Phase III
VA-003	Use of Roster of Veterans Who Served in Persian Gulf Area
VA-004	Boston Environmental Hazards Research Center Program
VA-004A	Evaluation of Cognitive Functioning of Persian Gulf Veterans
VA-004B	Evaluation of Neurological Functioning in Persian Gulf Veterans
VA-004C	Gulf War and Vietnam Veterans Cancer Incidence Surveillance
VA-004D	Evaluation of Respiratory Dysfunction Among GW Veterans
VA-004E	The Aromatic Hydrocarbon Receptor (AhR) as a Biomarker of Susceptibility
VA-004F	Validity of Computerized Tests
VA-005	East Orange Environmental Hazards Research Center Program
VA-005A	Health and Exposure Survey of Persian Gulf Veterans
VA-005B	Physiological and Psychological Assessments of Persian Gulf Veterans
VA-005C	Effects of Exertion and Chemical Stress on Persian Gulf Veterans
VA-005D	Effects of Genetics and Stress on Responses to Environmental Toxins
VA-006	Core Program: Portland Environmental Hazards Research Center: Environment, Veterans Health and the Gulf War Syndrome. Core Project for Clinical and Epidemiology Research
VA-006A	Psychosocial, Neuropsychological and Neurobehavioral Assessment (Project I)
VA-006B	Clinical and Neuroendocrine Aspects of Fibromyalgia (Project II)
VA-006C	Neurotoxicity of Environmental Pollutants and Warfare Agents (Project III)
VA-006D	DNA Damage from Chemical Agents and Its Repair (Project IV)
VA-006E	Clinical and Epidemiology Leishmania Research
VA-007	Desert Storm Reunion Survey
VA-008	Psychological Test Data of GW Veterans Over Time

- VA-009 Evaluation of Cognitive Functioning in Persian GW Veterans Reporting War-related Health Problems
- VA-010 Memory and Attention in PTSD
- VA-011 Neuropsychological Functioning in Veterans
- VA-012 Psychological Assessment of Operation Desert Storm Returnees
- VA-013 Neurobehavioral Aspects of Persian Gulf Experiences: A Pilot Study
- VA-015 Vaccine-Mediated Immunity Against Leishmaniasis
- VA-016 Protective Immunity in Experimental Visceral Leishmaniasis
- VA-017 Immunological Evaluation of Persian Gulf Veterans
- VA-018 Chronic Gastrointestinal Illness in Persian Gulf Veterans
- VA-020 Psychological Adjustment in Operation Desert Shield/Storm Veterans
- VA-021 A Comparison of PTSD Symptomatology among Three Army Medical Units Involved in ODS
- VA-036 Stress Symptoms and Their Causal Attribution in Desert Storm Veterans
- VA-040 Musculoskeletal Symptoms in Gulf War Syndrome
- VA-046 Diarrhea in Persian Gulf Veterans: An Irritable Bowel-Like Disorder
- VA-047 Retrospective Verification of Mustard Gas Exposure
- VA-048 Cross-Sensitization as a CNS Model for Gulf War Chemical Intolerance
- VA-049 Sensitivity to Pyridostigmine Bromide: Persistent Neural Dysfunction
- VA-050 Neuropsychological findings in a sample of Operation Desert Storm Veterans
- VA-051 Psychobiological Assessment of Desert Storm Veterans
- VA-053 Spouses and Children Program
- VA-054 Follow-up of Psychological and Neurocognitive Gulf War Outcome: Relation to Stress
- VA-055 Antibiotic Treatment of GW Veterans' Illnesses (ABT) (See also DoD-119)
- VA-056 Birmingham's GW Veterans' Illness Demonstration Clinic (13)
- VA-057 Case Management and Residential Rehabilitation for Persian GW Veterans (13)
- VA-058 Implementation and Evaluation of GW Veterans' Demonstration Project (13)
- VA-059 Demonstration Treatment Program for GW Veterans with Unexplained Physical Symptoms (13)
- VA-060 Identification and Management of Sleep Disorders in GW Veterans

- VA-061 An Epidemiological Investigation into the Occurrence of Amyotrophic Lateral Sclerosis (ALS) Among GW Veterans (See also DoD-118)
- VA-062 A Randomized, Multi-Center, Controlled Trial of Multi-Model Therapy in Veterans with Gulf War Illness (EBT) (See also DoD-115; formerly VA/DoD 1V)
- VA-063 VA/DoD Core Funding of the Medical Follow-Up Agency (See also DoD-116; formerly VA/DoD-2V/2D)
- VA-063A Follow-Up Investigation of Troops Exposed to Nerve Agents at Aberdeen Proving Ground (Pilot Study) (See also DoD-116A; formerly VA/DoD-2VA/2DA)
- VA-063B Patterns of Pre-Persian Gulf War Illness and Health Care Seeking Pilot Study (See also DoD-116B; previously VA/DoD-2VB)
- VA-064 Boston Environmental Hazards Research Center
- VA-064A Functional Neuroimaging in Lead Exposed Adults
- VA-064B Quantification and Validation of Structure-Function Relationships Through Visuospatial Test Performance
- VA-064C Development of a Structured Neurotoxicant Assessment Checklist (SNAC) for Clinical use in Veteran Populations
- VA-065 San Antonio Environmental Hazards Research Center
- VA-065A Does a Variant of the Human SOD2 Gene Increase Sensitivity to Hazards?
- VA-065B The Contribution of FEN-1 to Genetic Integrity Subsequent to Oxidative Stress
- VA-065C The Importance of Hydrogen Peroxide Detoxification in Cellular Protection
- VA-065D Do Defective Gpx1 and ALDH2 Genes Increase Sensitivity to Environmental Hazards?
- VA-066 Physiological Responding in Posttraumatic Stress Disorder
- VA-067 Olfactory Functioning in GW Veterans
- VA-068 Family Study of Fibromyalgia
- VA-069 Cardiovascular Hyporeactivity and Fatiguing Illness in GW Veterans
- VA-070 A Clinical Evaluation of the Health Status of Persian GW Veterans in VISN 8
- VA-071 Central Nervous System Modulation of Visceral Pain in the Persian Gulf Syndrome
- VA-072 Roles of Paraoxonase, Butyrylcholinesterase and Stress in Unexplained Illnesses
- VA-073 Pain Sensitivity in GW Veterans with Medically Unexplained Musculoskeletal Pain
- VA-074 A Randomized Clinical Trial for Cognitive-Behavioral Treatment for PTSD in Women (See DoD-125)
- VA-075 ALS and Veterans: Are Veterans at Increased Risk?
- VA-076 Analysis of Hippocampal Volume in Aging Combat Veterans with PTSD

- VA-077 HPA Axis Reactivity in Men and Women with Chronic PTSD
- VA-078 Millennium Cohort Study (See also DoD-143)
- VA-080 Neurochemical and Neurobehavioral Impact of Pyridostigmine Bromide Treatment and Stress
- VA-081 Stress, Pro-Inflammatory Cytokines and Coping Behavior
- VA-082 Pituitary Adrenal Function in People with Fatiguing Illness
- VA-083 Neuropsychological Assessment of a Population-Based Sample of Persian GW Veterans and Controls
- VA-084 Neurobiology of Severe Psychological Trauma in Women
- VA-085 Associative Learning in Veterans with and without Combat Experience
- VA-086 A Clinical Trial of Magnetic Stimulation in Depression
- VA-087 Improving Outcomes of Depression in Primary Care
- VA-088 Prospective Assessment of Neurocognition in Future Gulf-deployed and Gulf-nondeployed Military Personnel: A Pilot Study (See also DoD-154)
- VA-089 National Registry of Veterans with Amyotrophic Lateral Sclerosis
- VA-090 Differential Gene Expression in Pathologies Associated with Neuronal Hyperexcitability: Links to Gulf War Illness
- VA-090A Neuronal Hyperexcitability and Motor Neuron Regeneration
- VA-090B Gene Expression and Proteomic Strategies in Severe Psychiatric Disorders
- VA-090C Developmental Differences in Alcohol Withdrawal Sensitivity
- VA-090D Seizures and Neuroplasticity: Physiology and Biochemistry
- VA-091 The Role of Dietary Choline in Neuroprotection
- VA-092 Acetylcholinesterase Activity in GW Veterans
- VA-093 HPA Axis Alterations in PTSD: A Comparison of Gulf War and Vietnam Veterans
- VA-094 The Immunology of Chronic Cutaneous Leishmaniasis
- VA-095 The Role of Signal Regulatory Proteins in Astrocytomas
- VA-096 Functional Imaging of Pain in Veterans with Unexplained Muscle Pain
- VA-097 Improving a mM-CSF Tumor Vaccine for Established Intracranial Gliomas
- VA-098 Post-Transcriptional Gene Regulation of VEGF in Malignant Gliomas
- VA-099 Vaccination Against Visceral Leishmaniasis with a Multi-Epitope Vaccine
- VA-100 Studies of the Blood-Brain Barrier and it's Manipulation

- VA-101      Biomarkers Discovery in ALS
- VA-102      Cholinergic and Monoaminergic Influences on Sleep
- VA-103      Hypothalamic and Basal Forebrain Regulation of Sleep and Arousal
- VA-104      Characterization of Pain Processing Mechanisms in the Irritable Bowel Syndrome
- VA-105      Expression of the Major Surface Protease of Leishmania Chagasi
- VA-106      Interoceptive Stressor Conditioning: A Model for Gulf War Illness
- VA-107      Evaluation of Stress Response Systems in GW Veterans with CMI
- VA-108      Telemedicine Treatment for Veterans with Gulf War Illness
- VA-109      Effects of Stress on Memory: Brain Circuits, Mechanisms and Therapeutics
- VA-110      Pain Among GW Veterans: Secondary Analysis of CSP#458 Data
- VA-111      T-Cell Responses to Multiple Immunizations and Stress
- VA-112      National VA Amyotrophic Lateral Sclerosis Research Consortium
- VA-113      Novel Cause of Motor Neuron Disease
- VA-114      Strategies in Therapeutic Development of Neurodegenerative Diseases
- VA-115      Autonomic System Changes Cause Intestinal Symptoms in GW Veterans
- VA-116      Quantitative Trait Genes Controlling Circadian and Sleep Behaviors
- VA-117      Estimates of Cancer Prevalence in Gulf Veterans Using State Registries
- VA-118      Post War Mortality from Neurologic Diseases in Gulf Veterans, 1991-2004
- VA-119      Patterns of Microarray Gene Expression in Gulf War Illness
- VA-120      Arginase NO Synthase and Cell Death in Amyotrophic Lateral Sclerosis
- VA-121      Genes, Environment, and Oxidative Stress in Neurodegenerative Disorders
- VA-122      Role of Mitochondrial Oxidative Stress in ALS
- VA-123      Interactions Between Maternal Care, Stress and Pyridostigmine Bromide
- VA-124      Early Life Determinants of Vulnerability to Pyridostigmine Bromide
- VA-125      Effects of Gulf War Illness on Brain Structure, Function and Metabolism: MRI/MRS at 4 Tesla
- VA-126      Structural Magnetic Resonance Imaging in Gulf War-Era Veterans
- VA-127      Interactions of the Leishmania sp. with Mammalian Cells
- VA-128      MR Tracking of Stem Cells for Replacement Therapy in ALS



- VA-129      Glucocorticoid Responsivity in GW Veterans
- VA-130      Tissue Factor and Gulf War-Associated Chronic Coagulopathies
- VA-131      Neuroendocrine Regulators and Proteomics in GW Veterans with CMI
- VA-132      Immunologic Mechanisms and Biomarkers in Gulf War Illness
- VA-133      Longitudinal Study of Gene Expression and Gene Products in Veterans with Gulf War Illness
- VA-134      Autonomic Functions of GW Veterans with Unexplained Illnesses
- VA-135      Motor Neuron Function of GW Veterans with Excessive Fatigue
- VA-136      Central Mechanisms Modulating Visceral Sensitivity
- VA-137      Diarrhea-Predominant Irritable Bowel Syndrome in Persian Gulf Veterans
- VA-138      Inspiratory Flow Dynamics During Sleep in GWS and the Effect of CPAP
- VA-139      Sleep Neurobiology and Circuitry
- VA-140      Integrated Neuroimaging and Neuropathological Analysis of the Effects of Physical Activity on Progression and Therapy in ALS
- VA-141      Genetic Analysis of an Invertebrate Model of Amyotrophic Lateral Sclerosis
- VA-142      VA Gulf War Biorepository Trust
- VA-143      The Role of Protein Oxidation in the Progression of ALS
- VA-144      Testing the Role of Permethrin on the Progression of ALS
- VA-145      Proteomic Analysis of Cellular Response to Biological Warfare Agents
- VA-146      Direct Delivery of Neurotoxins to the Brain by an Intranasal Route
- VA-147      The Diagnosis and Pathogenesis of Occult Leishmaniasis
- VA-148      Profile of GW Veterans Who Applied for Undiagnosed Illness Compensation
- VA-149      Behavior of Neural Stem Cells in a Rat Model of GWS
- VA-150      GW Veterans Illnesses' Research IDIQ Contract with UTSW
- VA-151      Genetic Epidemiology of ALS
- VA-152      Multiple Sclerosis in GW Veterans
- VA-153      Bacterial Overgrowth Associated with Chronic Multi-Symptom Illness Complex
- VA-154      Imaging Pain Modulation in GW Veterans with Chronic Muscle Pain
- VA-155      Host Defense Mechanisms in Polyaromatic Hydrocarbon Carcinogenesis

- VA-156 Gulf War Era Cohort and Biorepository (CSP 585)
- VA-157 A Clinical Demonstration of an EEG Brain-Computer Interface for ALS Patients (CSP 567)
- VA-158 Testing the Feasibility of MC CBT for Veterans with IBS
- VA-159 Somatic hypersensitivity in Veterans with IBS
- VA-160 Lipoic Acid Therapy for Experimental Autoimmune Encephalomyelitis
- VA-161 Multiple Antigenic Peptides to Alter the Course of Autoimmune Disease
- VA-162 Transcription factors regulating sensory gene expression and pain pathways
- VA-163 Immunoregulation of Myelin Specific T Lymphocytes
- VA-164 Central Mechanisms Modulating Visceral Sensitivity (renewal of VA-136)
- VA-165 A Pilot Study of CPAP Adherence Promotion by Peer Buddies with Sleep Apnea
- VA-166 A Randomized Controlled Trial of a Mindfulness-Based Intervention for Gulf War Syndrome
- VA-167 Neuroprotection and Myelin Repair Mechanisms in Multiple Sclerosis
- VA-168 Sleep Neurobiology and Circuitry
- VA-169 Prevention of Hippocampal Neurodegeneration Due to Age and Apnea
- VA-170 Epigenetic Mechanisms Relevant to the Pathogenesis of ALS
- VA-171 Nanoparticle Coupled Antioxidants for Respiratory Illness in Veterans
- VA-172 Understanding Pain of Gastrointestinal Origin in Women that Serve in OEF/OIF
- VA-173 Impact of Exercise Training on Pain and Brain Function in GW Veterans
- VA-174 VA GW Veterans' Illnesses Biorepository
- VA-175 Memory and Mood Enhancing Therapies for Gulf War Illness
- VA-176 MEG Synchronous Neural Interactions (SNI) in GW Veterans
- VA-177 Somatic Hypersensitivity in Veterans with IBS
- VA-178 rTMS for the Treatment of Chronic Pain in GW1 Veterans
- VA-179 Vascular and Skeletal Muscle Function in Gulf War Veterans Illness
- VA-180 Diagnostic Utility of mtDNA Content and Exercise Challenge in Veterans with GWI
- VA-181 Transcranial, Light-Emitting Diode (LED) Therapy to Improve Cognition in GWVI
- VA-182 Consensus Case Definition for Chronic Multisymptom Illness in 1990-1991 Gulf War Veterans
- VA-183 Examination of Cognitive Fatigue in Gulf War Illness Using fMRI

- VA-184 Longitudinal Assessment of Gulf War Veterans with Suspected Sarin Exposure
- VA-185 Identification of Plasma Biomarkers of Gulf War Illness Using “omic” Technology
- VA-186 Gulf War Exposures and the Molecular Mechanisms of Paternal Reproductive Risk
- VA-187 Multimodal Biological Assessment of Gulf War Illness
- VA-188 Complementary Neurosteroid Intervention in Gulf War Veterans’ Illnesses
- VA-189 CAM in Veterans with Gulf War Illnesses
- VA-190 Cognitive Rehabilitation for Gulf War Illness
- VA-191 Novel Neurotrophic Therapies in an Optimized Mouse Model of GWVI
- VA-192 Women vs. Men with GWI: Differences in Computational Models and Therapeutic Targets
- VA-193 Neuroinflammation, Oxidative Stress, and Hippocampal Defects in Gulf War Illness
- VA-194 Health of Family Members: Secondary Analysis of CSP #458 Data
- VA-195 RCT of Duloxetine and Pregabalin for the Treatment of Gulf War Illness in Veterans
- VA-196 Immune Basis for Hippocampal Cholinergic Deficits in Pyridostigmine-Treated Rats
- VA-197 Genomics of Gulf War Illness in Veterans
- VA-198 Healthcare utilization patterns and associated costs for Gulf War I Era Veterans
- VA-199 Post exertion malaise in GWI - Brain autonomic and behavioral interactions
- VA-200 A Translational Medicine Approach to Gulf War Illness: From Cells to Therapy
- VA-201 WRIISC as a Model of Care for Chronic Multisymptom Illness
- VA-202 Gulf War neurotoxicants and acquired cognitive and neuropsychological dysfunction
- VA-203 Novel Interventions for Gulf War Veterans’ Illnesses
- VA-204 Pilot Test of Telephone-Delivered Cognitive Behavioral Therapy for Insomnia for Veterans with Gulf War Illness
- VA-205 A Randomized, Double-blind Placebo-controlled Phase III Trial of Coenzyme Q10 in Gulf War Illness